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Review article

Seeing beyond words: Visualizing autism spectrum disorder biomarker insights

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ABSTRACT

Objective: This study employs bibliometric and visual analysis to elucidate global research trends in Autism Spectrum Disorder (ASD) biomarkers, identify critical research focal points, and discuss the potential integration of diverse biomarker modalities for precise ASD assessment.
Methods: A comprehensive bibliometric analysis was conducted using data from the Web of Science Core Collection database until December 31, 2022. Visualization tools, including R, VOSviewer, CiteSpace, and gCLUTO, were utilized to examine collaborative networks, co-citation patterns, and keyword associations among countries, institutions, authors, journals, documents, and keywords.
Results: ASD biomarker research emerged in 2004, accumulating a corpus of 4348 documents by December 31, 2022. The United States, with 1574 publications and an H-index of 213, emerged as the most prolific and influential country. The University of California, Davis, contributed significantly with 346 publications and an H-index of 69, making it the leading institution. Concerning journals, the Journal of Autism and Developmental Disorders, Autism Research, and PLOS ONE were the top three publishers of ASD biomarker-related articles among a total of 1140 academic journals. Co-citation and keyword analyses revealed research hotspots in genetics, imaging, oxidative stress, neuroinflammation, gut microbiota, and eye tracking. Emerging topics included "DNA methylation," "eye tracking," "metabolomics," and "resting-state fMRI."
Conclusion: The field of ASD biomarker research is dynamically evolving. Future endeavors should prioritize individual stratification, methodological standardization, the harmonious integration of biomarker modalities, and longitudinal studies to advance the precision of ASD diagnosis and treatment.

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by a range of symptoms that

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encompass social interaction, communication, and behavior [1]. Notably, in the United States, the prevalence of ASD among 8-year--old children has risen from 1 in 68 in 2010 to 1 in 36 in 2020, highlighting the increasing global impact of ASD [2,3]. With approximately 78 million individuals worldwide affected by ASD, there is a growing urgency for innovative research and intervention efforts [4] since traditional diagnostic methods, primarily relying on clinical data and laboratory tests, have proven insufficient [5,6]. On average, ASD diagnoses occur after the age of 4 years of age, with 79 % of children receiving their diagnosis after starting school, thus missing crucial early intervention opportunities [7–9]. Consequently, there is a pressing need for innovative and precise diagnostic, monitoring, and intervention methods.

Recent advancements in ASD biomarker research have significantly enhanced our understanding of this complex condition. Various pivotal breakthroughs have emerged in key domains. Genetic biomarkers, identified through meticulous investigations, have unveiled critical genetic underpinnings contributing to the etiology of ASD [10,11]. Additionally, advanced neuroimaging techniques, including functional Magnetic Resonance Imaging(fMRI) and Diffusion Tensor Imaging (DTI), have elucidated intricate neural deviations and connectivity patterns specific to ASD, emerging as prospective diagnostic biomarkers of paramount significance [12–14]. Concurrently, behavioral biomarkers, pinpointed through precise eye tracking technologies, have revealed distinctive gaze patterns and socially relevant attentional behaviors exhibited by individuals with ASD [15,16]. Moreover, machine learning algorithms, adept at amalgamating diverse biomarker data, have demonstrated significant potential in enhancing the precision of ASD diagnosis and its predictive accuracy [17–19]. These collective research endeavors signify a noteworthy advancement toward early ASD detection, the customization of personalized treatment modalities, and a deeper understanding of the intricate biological underpinnings of the disorder, all aimed at improving the overall quality of life for individuals with ASD and their families.

However, ASD biomarker research faces challenges characterized by fragmented research efforts, difficulties in tracking research hotspots, and the complexity of integrating diverse research findings [20]. These limitations hinder the identification of robust biomarkers for clinical diagnosis and therapeutic interventions. In this context, the potential of bibliometrics and visual analysis stands out as remarkable. By systematically analyzing scientific literature, these methods can unveil collaboration networks and research

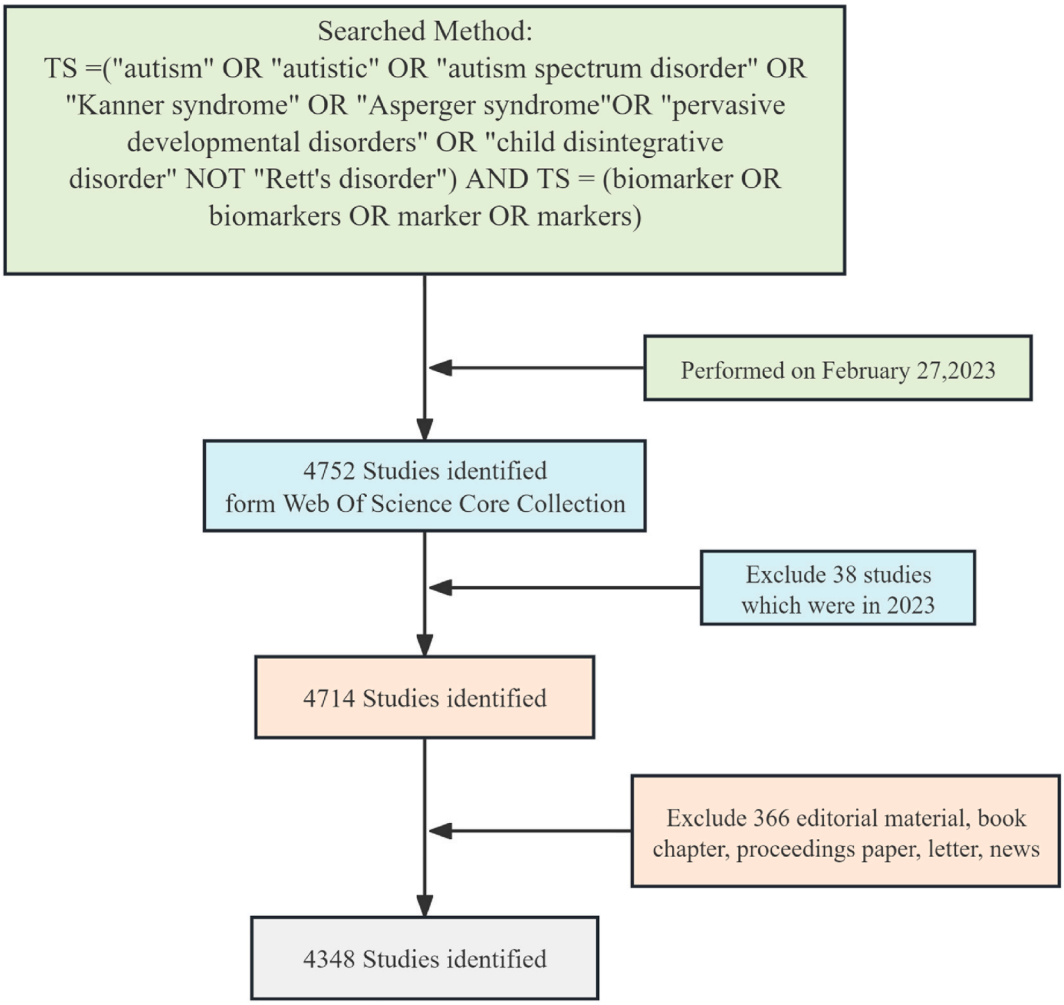

Fig. 1. The data collection and retrieval strategy.

hotspots within the field [21]. Bibliometrics and visual analysis are widely employed in the medical field, providing valuable insights for research endeavors [22,23].

In this paper, we employed bibliometric analysis and visualization software, including R, VOSviewer, CiteSpace, and gCLUTO, to explore collaboration patterns, research hotspots, and trends in ASD biomarker research. Furthermore, based on these analyses, we discussed the integration of data from multiple biomarker modalities to assess the distinct and unique characteristics of ASD more accurately. Finally, we have highlighted the current challenges in biomarker approaches and provided recommendations for enhancing ASD biomarker research.

2. Methods

2.1. Data collection

The Web of Science Core Collection (WOSCC) is widely recognized as a comprehensive academic literature retrieval tool, introduced by Clarivate Analytics and regarded globally as one of the most significant and influential scholarly citation databases [24]. To ensure the integrity and representativeness of our data, we opted to employ this database for our literature search. Within the WOSCC, we formulated a series of effective literature search strategies: TS = ("autism" OR "autistic" OR "autism spectrum disorder" OR "Kanner syndrome" OR "Asperger syndrome" OR "pervasive developmental disorders" OR "child disintegrative disorder" NOT "Rett's disorder") AND TS = (biomarker OR biomarkers OR marker OR markers). To mitigate any potential bias arising from the database's daily updates, we specifically chose the search date as February 27, 2023.

Following the search, we retrieved a total of 4752 articles. Subsequently, we excluded articles from the year 2023, resulting in the removal of 38 articles from the analysis. Thereafter, we subjected these articles to meticulous screening. We began by excluding items such as letters, revised versions, book chapters, conference papers, editorial materials, news articles, and publications, ensuring the accuracy and representativeness of our screening results. Post-screening, we were left with a final set of 4348 articles, comprising 3632 articles of the "Article" type and 716 articles categorized as "Review". The data collection and retrieval strategy process is shown in Fig. 1. These selected articles will serve as a rich source of data and valuable references for our ASD biomarker research.

2.2. Data analysis

This study employed a variety of widely recognized bibliometric analysis tools, including R, VOSviewer, CiteSpace, and gCLUTO. These software applications are esteemed in the academic community and offer distinct capabilities in the field of literature analysis and visualization. R, an open-source programming language and environment, was used to conduct comprehensive bibliometric analysis. Through the utilization of the Bibliometrix package integrated within R, researchers were able to perform robust statistical analysis and visualization of key data parameters [25], such as publication trends, affiliations, authors, citations, and keywords. This comprehensive analytical suite provided researchers with a thorough understanding of the research landscape. VOSviewer, a potent visual analysis software developed by vaneck and Waltman (2010) at Leiden University's Centre for Science and Technology Studies, excels in revealing collaboration networks among countries, institutions, and authors based on co-occurrence relationships [26]. By

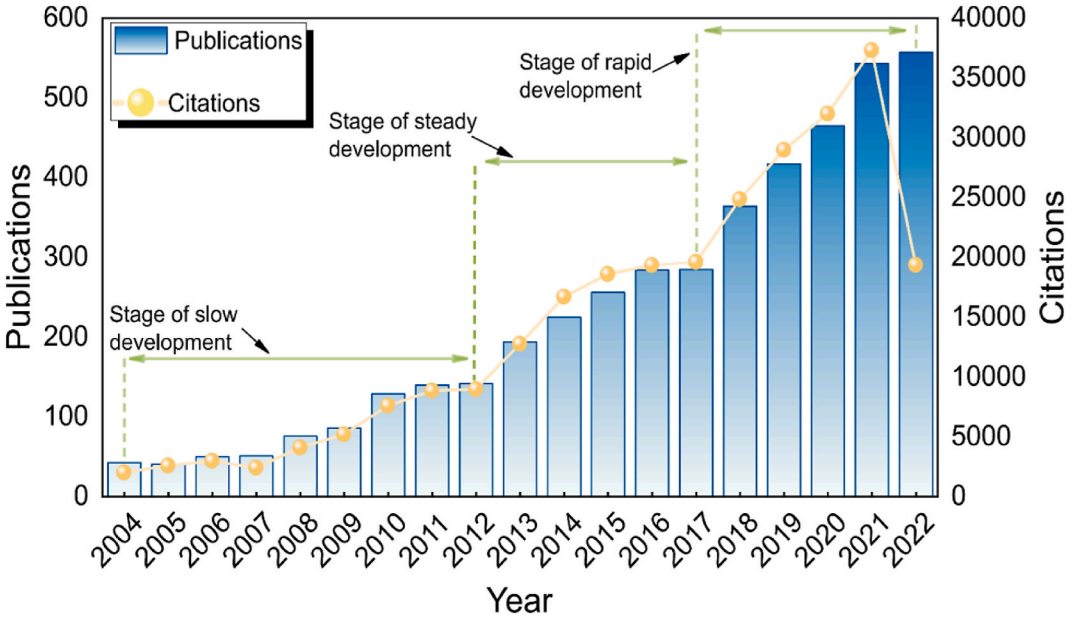

Fig. 2. Global publication output and citation trend on biomarker research in ASD from 2004 to 2022.

leveraging co-occurrence, VOSviewer facilitated the identification of collaboration patterns, research focal points, and the evolving scholarly landscape. CiteSpace, another indispensable tool, offers detailed insights into literature evolution and key research pathways. Renowned for its ability to identify pivotal turning points and emerging research frontiers, CiteSpace generates visualizations such as co-citation networks and temporal evolution graphs. This aids in gaining a nuanced understanding of the chronological progression within a specific field [27]. gCLUTO proved invaluable in refining keyword selection and enabling keyword matrix biclustering analysis, optimizing the process of information retrieval.

3. Results

3.1. Global trend in publication outputs and citations

From 2004 to 2022, as depicted in Fig. 2, the trajectory of global publications and cumulative citations in ASD biomarker research unfolds. Notably, the advancement of biomarkers in the ASD field has been remarkable, with a pronounced surge in the last five years, comprising 53.9 % (2346 out of 4348) of the total publications. The annual global publication count has surged from 43 in 2004 to 557 in 2022, exhibiting an annual growth rate of 12.26 %. As of the search date (February 27, 2023), the collective articles have garnered 274,368 citations, translating to an annual average of 14,440.42 citations since their publication, equating to an average of 63.10 citations per document. It is noteworthy that the current research endeavors continue to thrive in a phase of continuous expansion.

3.2. Distribution of countries/regions

The exploration of biomarkers in ASD has garnered widespread global attention, with research contributions originating from 92 countries/regions, primarily concentrated in North America, Western Europe, East Asia, and other regions. Table 1 presents a ranking of the top ten countries/regions by publication output. Leading in terms of research activity, the United States (1574 publications, 36.201 %) emerged as the most prolific producer, followed by China (392 publications, 9.016 %) and the United Kingdom (278 publications, 6.394 %). The distribution of citations across these countries is depicted in Fig. 3A, while the global collaboration dynamics are portrayed in Fig. 3B and C. The United States outshines others in terms of citation count (71,385 times) and the highest H-index (213), outpacing the United Kingdom (12,100 times).

The landscape of international collaboration can be assessed through the Total Link Strength (TLS), a metric used in the VOSviewer software to evaluate the strength of inter-country collaboration, accounting for the volume of cross-border articles. The network co-occurrence map (Fig. 3C) highlights the leading countries in TLS, namely the United States (TLS = 1181), United Kingdom (TLS = 780), and Germany (TLS = 550). The SCP/MCP indices, derived from R, represent the count of publications co-authored by authors of the same/different nationalities. The MCP-Ratio signifies the proportion of transnational cooperation, which effectively identifies countries with lower publication numbers but a focus on global engagement. Among these, the United Kingdom (MCP-Ratio = 0.493), Germany (MCP-Ratio = 0.449), and Canada (MCP-Ratio = 0.396) stand out (Fig. 3B), highlighting their proclivity to transcend geographical boundaries and embrace worldwide collaboration.

3.3. Contributions of institutions

A total of 4757 institutions have made substantial contributions to the realm of ASD biomarker research. This profound collaboration is delineated in Table 2, showcasing the top ten prolific establishments, with seven domiciled in the United States. Notably, the University of California, Davis (346 publications), spearheaded the list in terms of productivity, closely trailed closely by King's College London (267 publications) and King Saud University (226 publications). By establishing a threshold of a minimum of 30 articles published by institutions, 52 such institutions emerged, as illustrated in Fig. 4. While varying degrees of collaboration exist among these institutions, a stable bidirectional or multi-directional cross-cooperation nexus is yet to be fully established. Within these 52 institutions, the University of Toronto stands out with the most significant number of collaborative partners (n = 41), closely followed by the University of California, Davis (n = 39), and Harvard Medical School (n = 38).

Table 1
The top 10 productive countries/regions.

Rank	Country	Counts	Percentage	H-index	SCP	MCP	MCP-Ratio	TLS	Total citations	Average citation per paper
1.	USA	1574	36.201	213	1268	306	0.194	1181	71,385	45.35
2.	China	392	9.016	58	280	112	0.286	326	5504	14.04
3.	UK	278	6.394	89	141	137	0.493	780	12,100	45.53
4.	Italy	248	5.704	78	158	90	0.363	526	6668	26.89
5.	Canada	149	3.427	75	90	59	0.396	410	5754	36.82
6.	Japan	140	3.220	63	119	21	0.15	97	3054	21.81
7.	Australia	131	3.013	59	95	36	0.275	331	5386	5.18
8.	France	120	2.760	67	76	44	0.367	414	2597	21.64
9.	Germany	107	2.461	49	59	48	0.449	550	2336	21.83
10.	India	103	2.369	27	90	13	0.126	101	1033	10.03

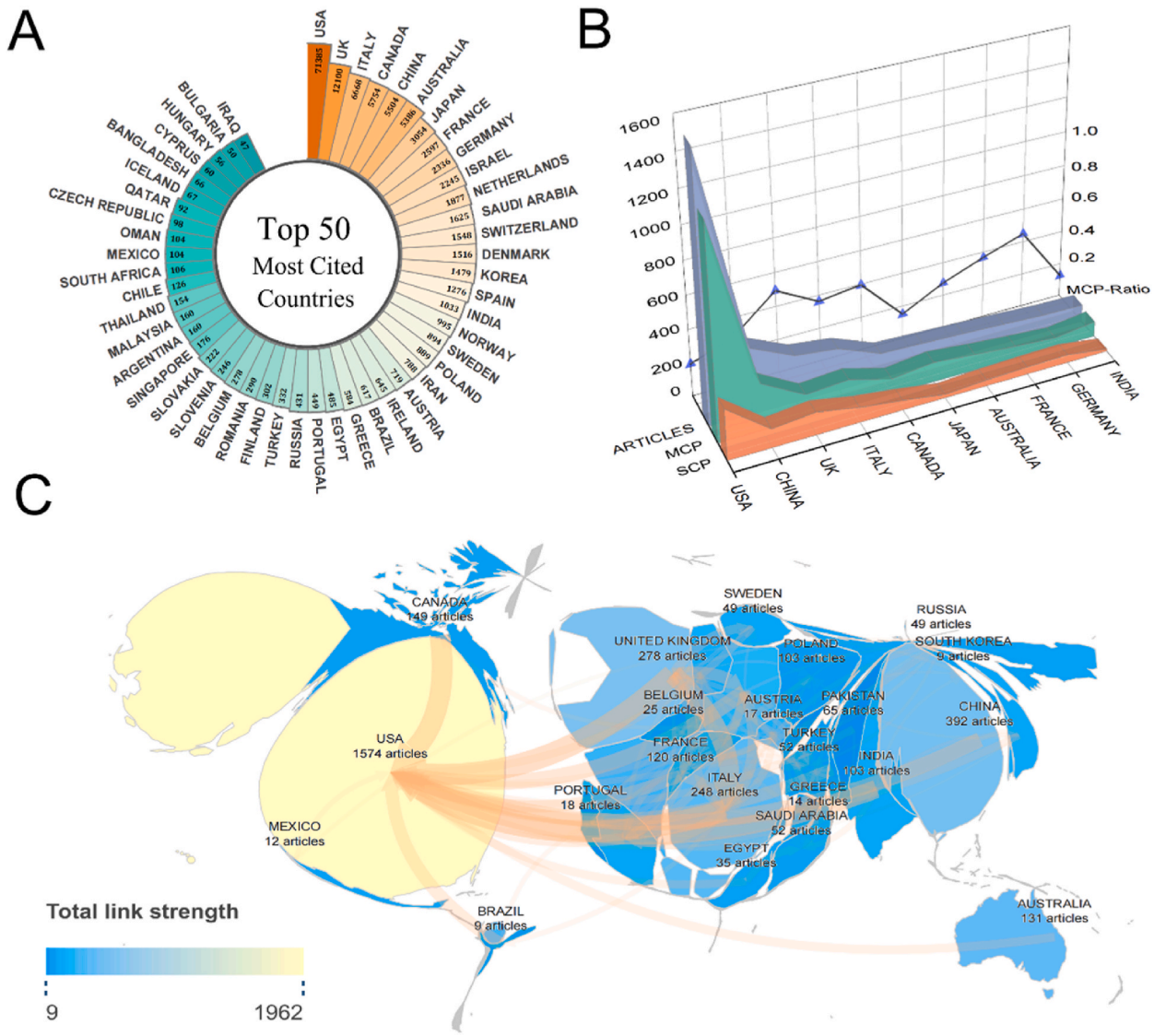

Fig. 3. The co-authorship network of countries/regions.

Table 2
The top 10 productive institutions.

Rank	Institution	Country	Counts	Percentage	H-index	TLS
1.	University of California, Davis	USA	346	7.958	69	287
2.	King's College London	UK	267	6.141	56	709
3.	King Saud University	Saudi Arabia	226	5.198	35	108
4.	Vanderbilt University	USA	186	4.278	43	230
5.	university of california los angeles	USA	175	4.025	43	377
6.	Harvard Medical School	USA	165	3.795	43	565
7.	University of Toronto	Canada	149	3.427	55	493
8.	Johns Hopkins University	USA	141	3.242	37	275
9.	University of Pennsylvania	USA	138	3.174	40	301
10.	Harvard University	USA	134	3.082	56	303

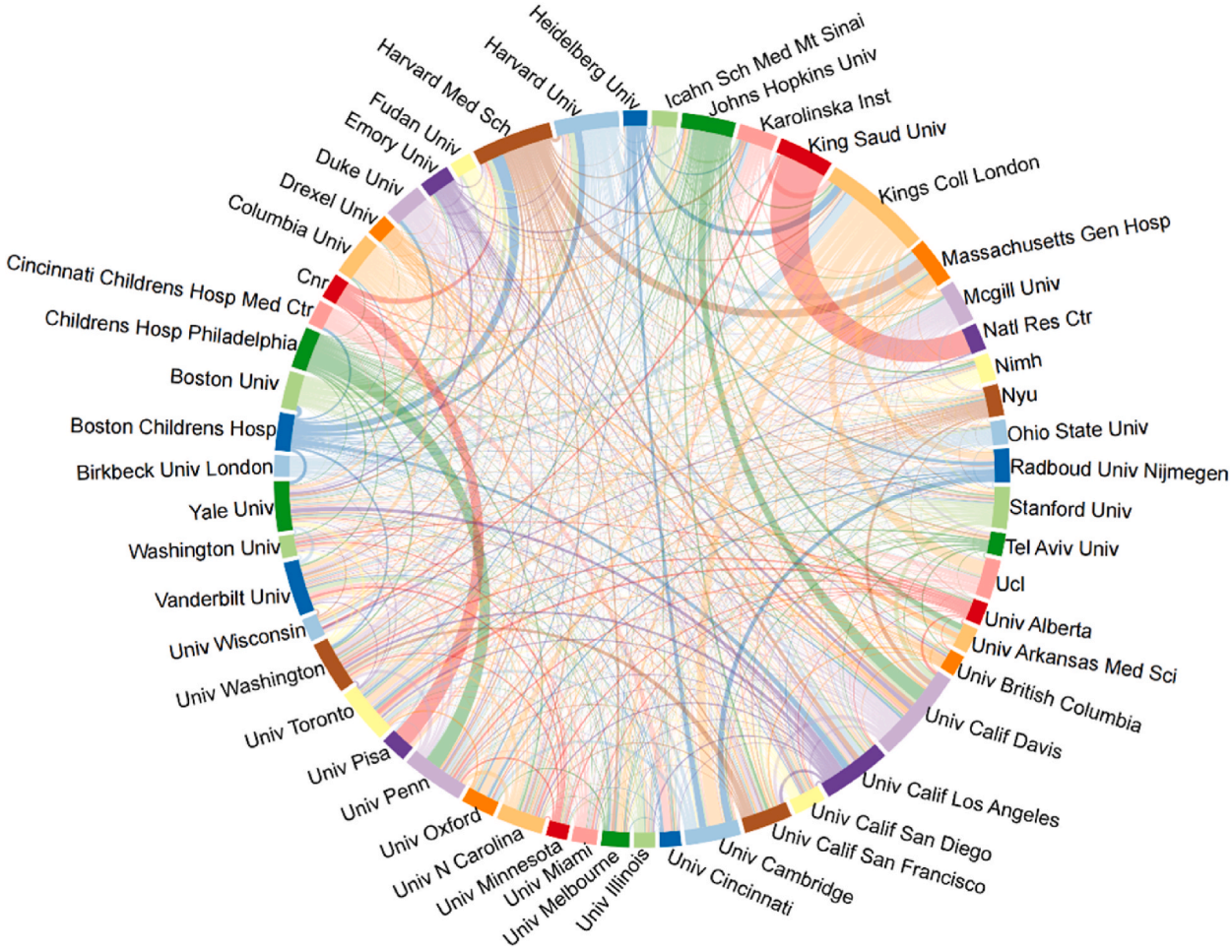

Fig. 4. The co-authorship network of institutions.
Note: The curved segments outside the circle represent institutions, with the size of the curved segments indicating the volume of publications. The connecting lines between curved segments represent collaborative relationships between institutions, with wider lines indicating more frequent collaborations.

3.4. Distribution and co-authorship of authors

The comprehensive covered encompassed a total of 19,192 authors, with an average collaborative effort comprising approximately seven authors per paper. Table 3 meticulously outlines the top 10 authors in terms of productivity. Evidently, El-Ansary, Afaf (47 publications, 343 citations) emerged as the most prolific, closely trailed by Charman, Tony (42 publications, 368 citations) and Hertz-Picciotto, Irva (36 publications, 218 citations). Delving into the co-authorship analysis employing VOSviewer, a stringent criterion of a minimum of 10 articles published by the author was applied, leading to the identification of 109 authors who meet this criterion. This

Table 3
The top 10 productive authors.

Rank	Author	Counts	Percentage	Institutions	H-index	TLS	Total citations
1.	El-Ansary, Afaf	47	1.081	King Saud University	16	90	343
2.	Charman, Tony	42	0.966	King's College London	22	293	368
3.	Hertz-Picciotto, Irva	36	0.828	University of California Davis	17	127	218
4.	Al-Ayadhi, Laila Y.	35	0.805	King Saud University	14	64	356
5.	Frye, Richard	35	0.805	University of Arizona	21	57	727
6.	Baron-Cohen, Simon	34	0.782	University of Cambridge	22	214	211
7.	Bolte, Sven	33	0.759	Curtin University	18	216	204
8.	Dawson, Geraldine	33	0.759	Duke University	16	243	200
9.	Johnson, Mark H.	30	0.690	University of London	19	161	329
10.	Croen, Lisa A.	28	0.640	University of California Davis	14	124	368

insightful co-authored analysis is visually represented in Fig. 5, wherein 90 authors are distinctively clustered into seven color-coded cohorts. Impressively, the author group centering on Dawson, Geraldine stood as the largest cluster. Remarkably, Bourgeron, Thomas holds the distinction of having the most co-authoring partners (n = 27), followed by Bolte, Sven (n = 23) and Charman, Tony (n = 22).

3.5. Distribution of source journals and top 10 high-cited articles

In comprehensive analysis, we identified a corpus of 4348 articles hailing from 1140 distinct journals. Table 4 meticulously catalogues the top ten journals in terms of publication volume, collectively amassing a noteworthy 921 articles—constituting approximately 21.18 % of the overarching publication count. Among these, the Journal of Autism and Developmental Disorders (n = 158), Autism Research (n = 137), and PLOS ONE (n = 106) distinctly emerge as prolific contributors. Noteworthy are Molecular Autism (H-index = 37, Impact Factor = 6.476) and Molecular Psychiatry (H-index = 35, Impact Factor = 13.437), which have achieved commendable H-indices and Impact Factors, unequivocally propelling the field's advancement. Fig. 6A chronicles the publication trends of the top ten journals from 2004 to 2022, with Autism Research and Frontiers in Psychiatry displaying increased publication activity in recent years—a telltale sign of heightened interest in this domain.

An examination of the citation patterns that research disseminated in journals associated with "MOLECULAR, BIOLOGY, IMMUNOLOGY" and "PSYCHOLOGY, EDUCATION, HEALTH" demonstrates a propensity to reference works from the "MOLECULAR, BIOLOGY, GENETICS" and "PSYCHOLOGY, EDUCATION, SOCIAL" domains. This suggests a robust and relatively steady knowledge framework within the purview of the study(Fig. 6B). Furthermore, it is discernible that publications in the "MEDICINE, MEDICAL, CLINICAL" realm are notably influenced by contributions from the "MOLECULAR, BIOLOGY, GENETICS" sphere.

The cumulative authoritative citations derived from the amalgamation of 4348 articles amount to 16,484, wielding a global citation count of 138,592. Intriguingly, the top ten cited articles exhibit individual authority citations ranging from 76 to 182, with global citations spanning 137 to 1196. Foremost among them is the article titled "Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism," featured in The American Journal of Clinical Nutrition. The study is

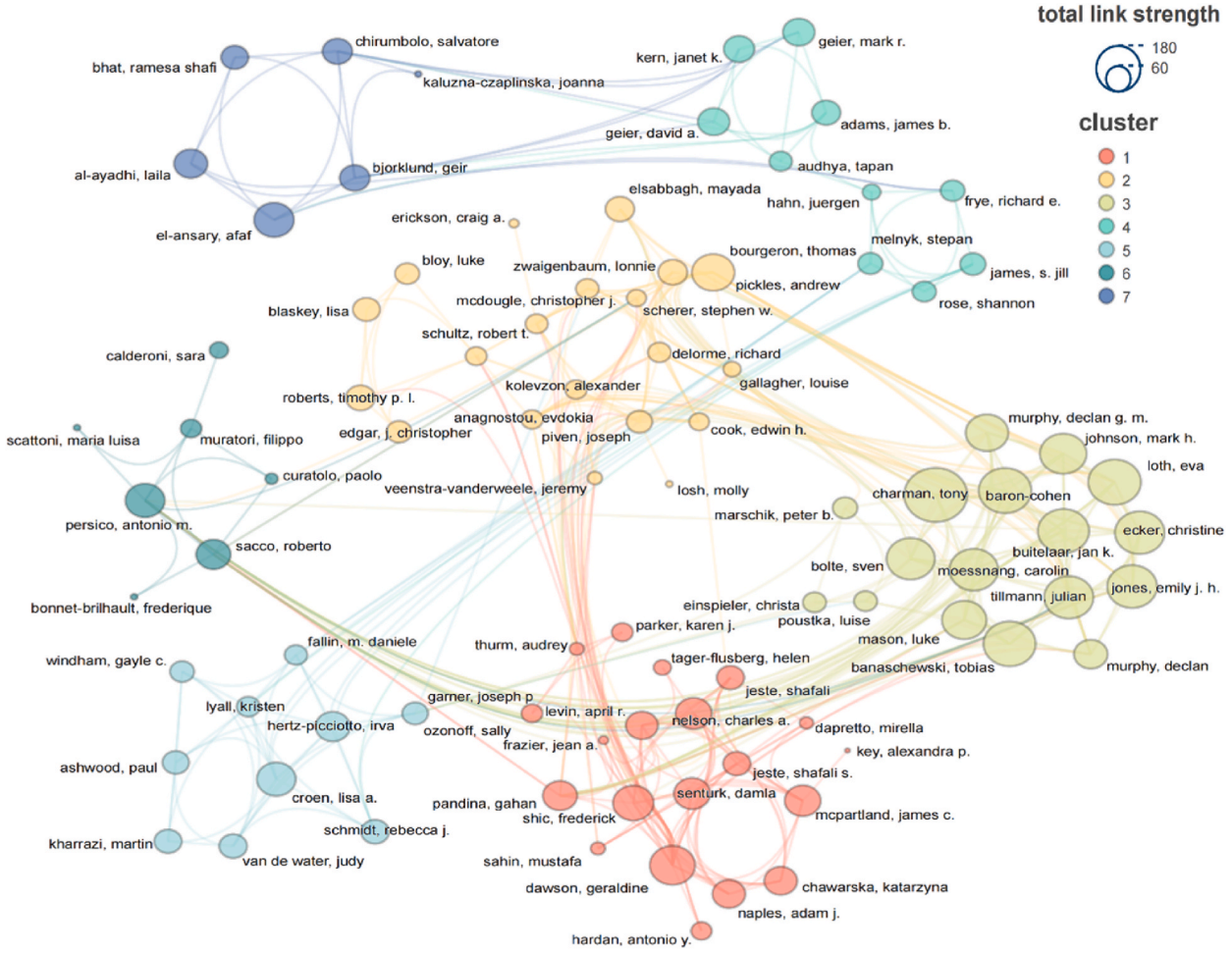

Fig. 5. The co-authorship network of authors.

Table 4
The top 10 productive journals.

Rank	Journal	Countries	Count	IF (2023)	JCR (2023)	H-index	Total citations	Percentage
1.	Journal of Autism and Developmental Disorders	USA	158	3.9	Q1	35	1368	3.634
2.	Autism Research	USA	137	4.7	Q1	29	2613	3.151
3.	PLOS ONE	USA	106	3.7	Q2	35	3653	2.438
4.	Molecular Autism	UK	92	6.2	Q1	37	3680	2.116
5.	Scientific Reports	UK	84	4.6	Q2	22	1542	1.932
6.	Translational Psychiatry	USA	79	6.8	Q1	31	3222	1.817
7.	Frontiers in Psychiatry	Switzerland	78	4.7	Q2	16	908	1.794
8.	Frontiers in Neuroscience	Switzerland	66	4.3	Q2	18	2111	1.518
9.	Molecular Psychiatry	UK	66	11.0	Q1	35	1138	1.518
10.	Journal of Neurodevelopmental Disorders	Scotland	55	4.9	Q1	19	1368	1.265

predominantly anchored in the metabolic profiles of autistic children, unveiling a diminution in methylation capacity and an elevation in oxidative stress relative to control subjects. Remarkably, a successful nutritional intervention trial involving folinic acid, betaine, and methylcobalamin rectified these imbalances, thereby underscoring the potential contribution of reduced methylation and heightened susceptibility to oxidative stress in the genesis of autism [28].

3.6. Analysis of top co-cited references

In our study, a total of 162,721 references have been meticulously cited, underscoring the robust scholarly support underpinning our investigation. Fig. 7a presents a schematic representation of the co-citation network analysis in the referenced study. The analytical outcomes reveal a Modularity Q value of 0.7339 and a Weighted Mean Silhouette score of 0.8842, demonstrating a robust clustering effect and superior clustering quality. Employing 162,721 co-cited references across a timeframe spanning from 2004 to 2022, with each year serving as a discrete time slice, CiteSpace selects the top 10 % of the most frequently cited references for group representation in co-citation analyses (as depicted in Fig. 7b). These co-cited references are further illustrated in the timeline map of Fig. 7b, which delineates the temporal development and progression of research within each cluster. The clustering analysis segregates the research into fifteen distinct clusters. Notably, “Metabolomics” (#0) emerges as the most substantial cluster, with “Haplotype Analysis” (#7) reflecting the foundational research themes within this domain. Presently, the research focal points have shifted towards "DNA Methylation" (#8), "Eye Tracking" (#2), "Metabolomics" (#0), and "Resting State fMRI" (#6). This transition underscores the growing scientific endeavor towards uncovering biomarkers for ASD, reflecting a broader engagement with the biological underpinnings of the disorder.

3.7. Keywords analysis of research hotspots

The selected keywords effectively encapsulate the primary themes of the publications, providing a solid foundation for conducting a cluster analysis based on their frequency of appearance. Following the exclusion of search-related terms, noteworthy keywords such as "EEG" (144 occurrences), "Schizophrenia" (142 occurrences), "Oxidative Stress" (135 occurrences), "ADHD" (130 occurrences), and "fMRI" (116 occurrences) emerge as the top five most frequently occurring keywords. Employing Bicomb and gCLUTO, we undertook the extraction and clustering of the top 100 keywords in our study, resulting in the emergence of eight distinct clusters, as depicted in Fig. 8A. This figure offers insights into the similarity among keywords within each cluster. Fig. 8B showcases a biclustering heatmap, generated from a binary matrix created for the top 100 keywords. This heatmap not only provides multifaceted clustering insights but also reflects the significance of individual keywords as well as those within the same clusters. Cluster 0, characterized by minimal internal variability, signifies optimal keyword clustering performance and primarily encompasses biomarkers within the realms of neuroimaging and machine learning. Cluster 1 predominantly addresses comorbidities linked with ASD. Cluster 2 centers around biomarkers associated with inflammation, immunity, and cytokines. Cluster 3 sheds light on the applications and target subjects of ASD biomarker research. Cluster 4 encompasses biomarkers related to metabolism, oxidative stress, and mitochondrial functionality. Cluster 5 delves into genetic and molecular biomarkers. Clusters 6 and 7 demonstrate heightened internal variability, encompassing ASD core symptoms, proteomics, electroencephalogram (EEG), and eye tracking biomarkers, contributing to a diverse exploration of ASD research dimensions.

4. Discussion

4.1. Global trends in ASD biomarker research

The surge in publications within the realm of ASD biomarker research over recent years constitutes a noteworthy and substantial phenomenon. This surge is emblematic of the increasingly acknowledged significance of early diagnosis and intervention for individuals affected by ASD, unwavering the unwavering commitment of researchers on a global scale as they grapple with the multifaceted challenges inherent to ASD. The extraordinary surge witnessed in ASD biomarker research, particularly in the last five years, representing more than half of the total publications, serves as an unequivocal indicator of the burgeoning worldwide influence

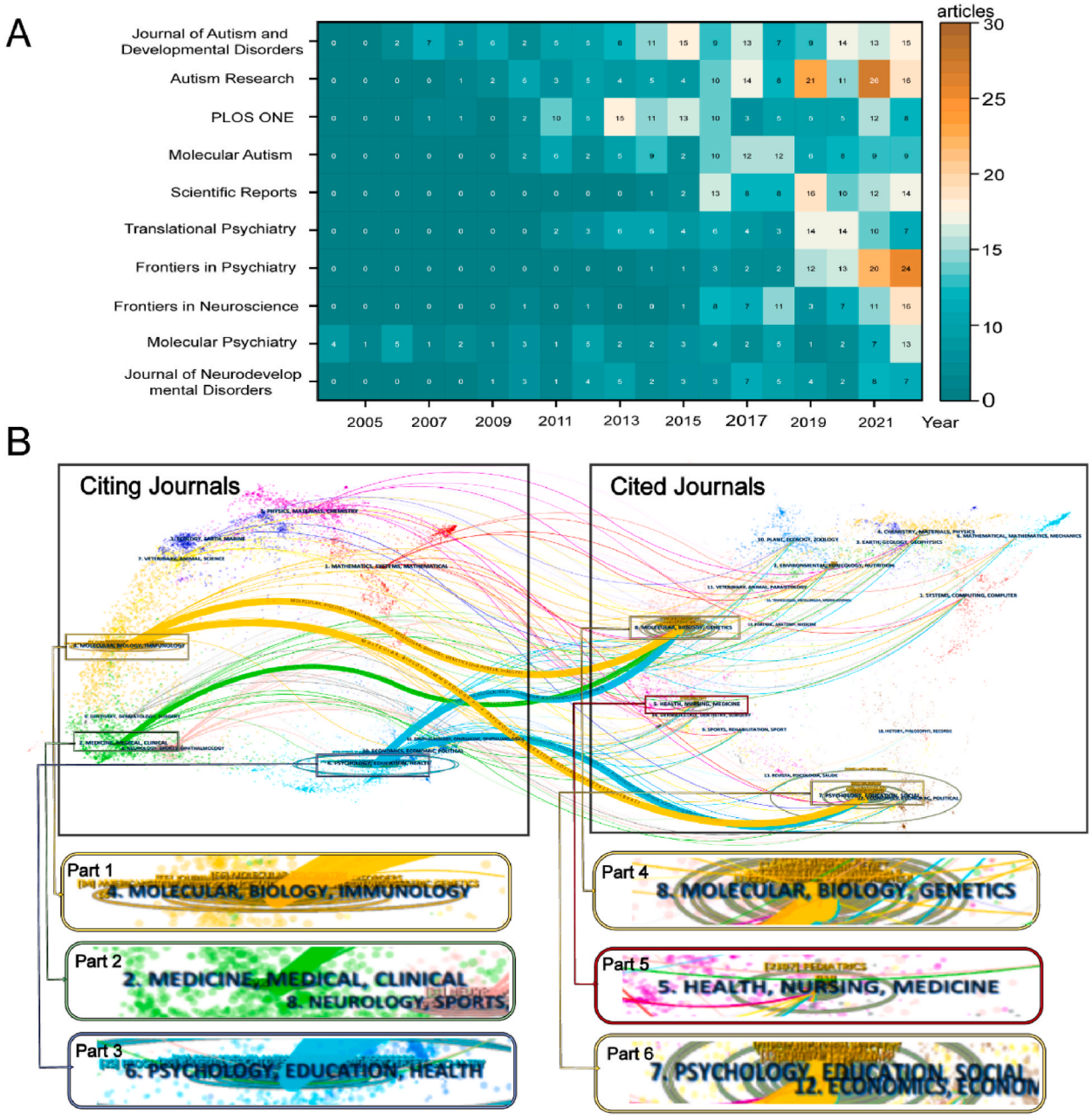

Fig. 6. Heatmap of annual publication distribution for top 10 journals (A) and overlay of journal pairings (B).

of this research field. This surge undeniably underscores the compelling need for pioneering research and interventions aimed at enhancing the quality of life for individuals living with ASD.

The emergent trend of global collaboration within this field is a highly encouraging and promising trajectory. Collaborative initiatives facilitate the amalgamation of diverse expertise and resources, ultimately expediting the pace of advancements in ASD biomarker research. Of particular note is the influential role occupied by the United States, both in terms of productivity and citations, signifying the global leadership it has assumed in advancing our collective understanding of ASD. Diverse institutions and authors have made commendable and substantial contributions to this research landscape, with specific institutions and authors gaining prominence due to their exceptional productivity and extensive engagement in collaborative endeavors. The identification of these prolific institutions and authors underscores the inherently cooperative nature of ASD biomarker research, an indispensable element for comprehensively addressing the multifaceted dimensions of ASD.

It is worth emphasizing that these collaborative efforts transcend geographical boundaries, accentuating the intrinsically global nature of ASD research. Furthermore, the eminence of certain journals, particularly those with high Impact Factors, highlights the

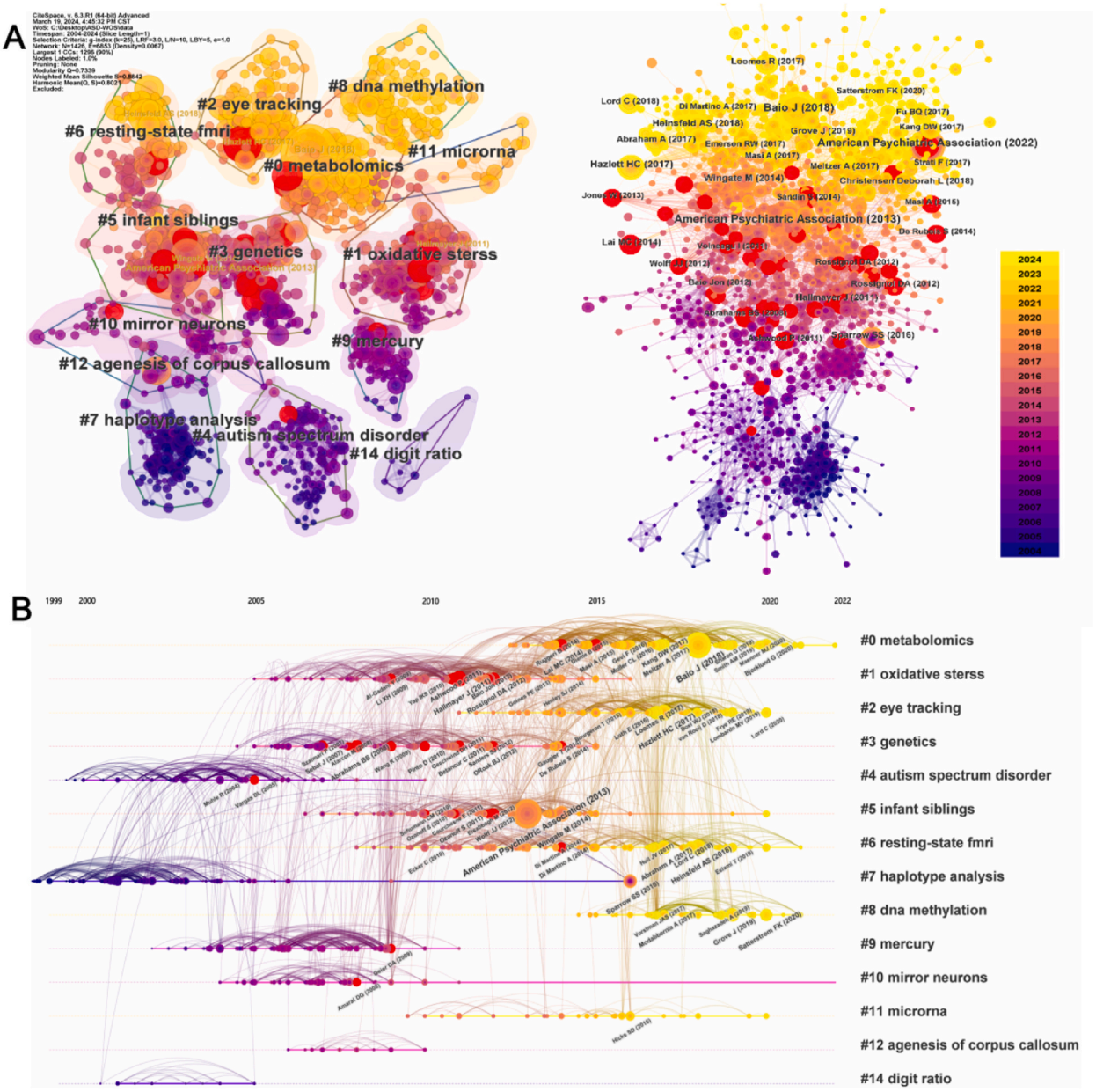

Fig. 7. Cluster View of Co-cited References from 2004 to 2022
Note: Image A depicts the cluster view of co-cited references, where temporal evolution is illustrated through lines of distinct colors. Nodes along these lines represent the cited references, with the node size reflecting the citation frequency of the literature. Nodes in deep red indicate strong citation bursts, highlighting periods where related research has been extensively cited. Image B shows a timeline map of co-cited literature clusters, with cluster numbers on the Y-axis and the years of citation publication on the X-axis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

pivotal role played by reputable outlets in effectively disseminating research findings. Such high-caliber publications are essential for propelling the field forward and garnering recognition within the broader scientific community. This comprehensive discussion underscores the dynamic and evolving landscape of ASD biomarker research while underscoring the paramount importance of international collaboration and the rigorous dissemination of findings to advance our collective understanding of ASD.

4.2. Hotspots and future directions in ASD biomarker research

The co-citation analysis of references is a potent tool for uncovering the research background, shifts, and trends in ASD biomarker studies. As illustrated in Fig. 7, references concerning DNA methylation, eye tracking, metabolomics, and resting-state fMRI have

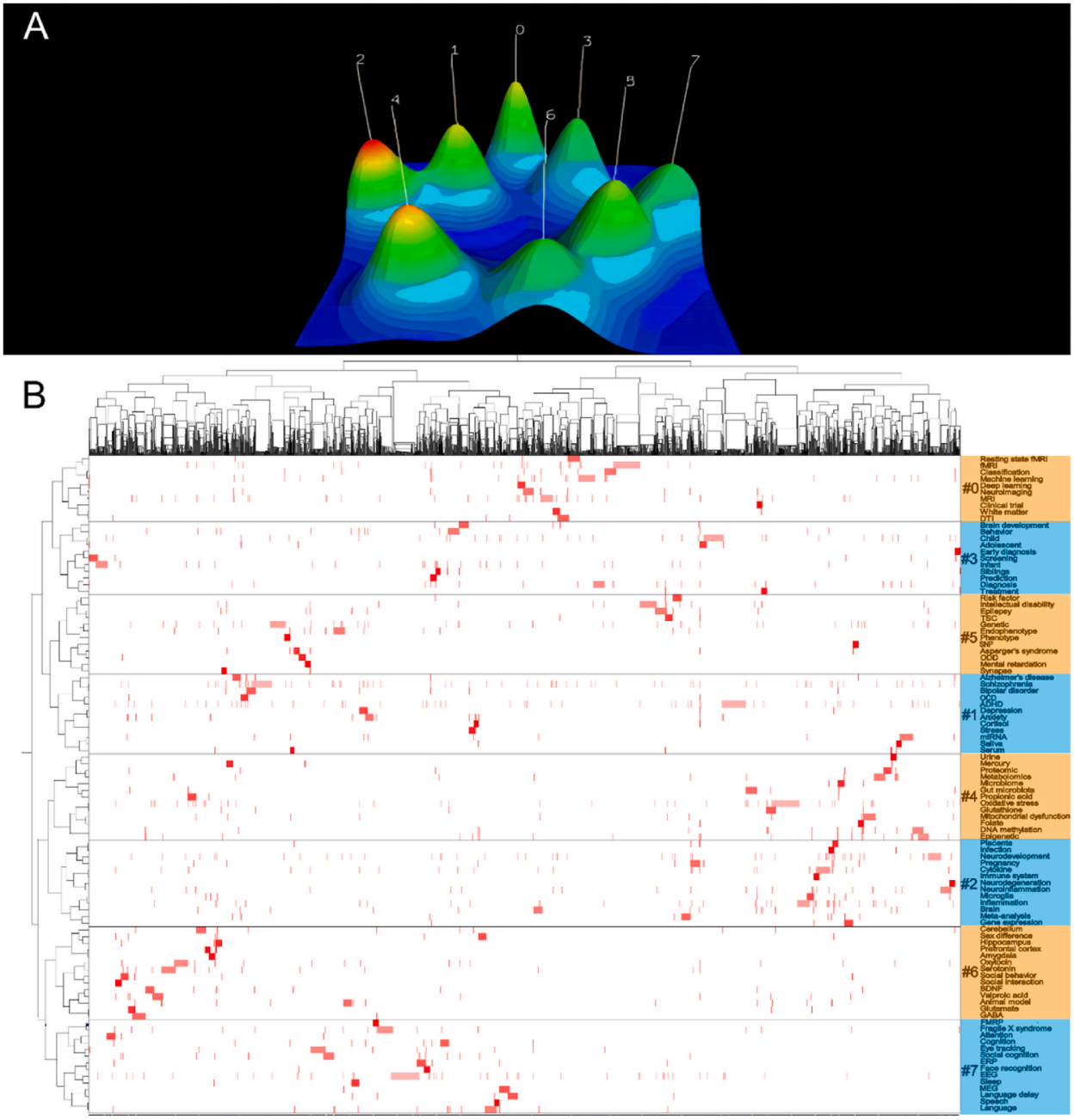

Fig. 8. Visualization of Bi-clustering Analysis for the Top 100 Keywords

Note: Panel A illustrates the bi-clustering analysis of keywords using a landscape representation with peaks and hills. Each hill corresponds to a cluster of keywords, with the size of the hill proportional to the number of keywords within the cluster. The color at the crest of each hill correlates with the intra-cluster deviation, where red signifies low variability and blue indicates high variability of keywords within the cluster. In Panel B, the bi-clustering analysis is presented as a heatmap. The columns represent the sequence of article appearances for keywords, while the rows indicate the keywords and their respective clusters. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

garnered substantial citations over the last five years, signifying their significance as scholarly reference points. Highly cited articles and keywords offer a means of categorizing research focal points and knowledge frameworks within the domain. Table 5 presents the top 10 most cited articles, that encompass biomarkers linked to physiological anomalies, behavioral manifestations, and the nutritional and metabolic status of ASD. Notably, five of these articles delve into aspects of oxidative stress. Fig. 8 depicts the cluster analysis of the foremost 100 keywords, accentuating the salient areas and themes of ASD biomarker research. In this context, it can be observed that

Table 5
The top 10 highest cited articles.

Number of local/global citations	First author	Title	Journal	IF (2023)	JCR (2023)	Year	Type of paper	Ref.
182/636	James SJ	Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism	The American Journal of Clinical Nutrition	7.1	Q1	2004	Clinical Study	[28]
123/467	Rossignol DA	Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis	Molecular Psychiatry	11.0	Q1	2012	Systematic Review	[29]
111/983	Zwaigenbaum L	Behavioral manifestations of autism in the first year of life	International Journal of Developmental Neuroscience	1.8	Q4	2005	Longitudinal Study	[30]
97/1196	Voineagu I	Transcriptomic analysis of autistic brain reveals convergent molecular pathology	Nature	64.8	Q1	2011	Experimental Study	[31]
96/328	Rossignol DA	A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures	Molecular Psychiatry	11.0	Q1	2012	Review	[32]
94/237	Frustaci A	Oxidative stress-related biomarkers in autism: Systematic review and meta-analyses	Free Radical Biology and Medicine	7.4	Q1	2012	Review	[33]
87/287	ROSE S	Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain	Translational Psychiatry	6.8	Q1	2012	Clinical Study	[34]
82/765	MUHLE R	The Genetics of Autism	Pediatrics	8.0	Q1	2004	Review	[35]
80/137	AL-GADANI Y	Central nervous system Metabolic biomarkers related to oxidative stress and antioxidant status in Saudi autistic children	Clinical Biochemistry	2.8	Q2	2009	Clinical Study	[36]
76/232	ADAMS J B	Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity	Nutrition and Metabolism	4.5	Q2	2011	Clinical Study	[37]

the hotspots of ASD biomarkers primarily revolve around the following six areas: genetics, imaging, oxidative stress, neuroinflammation, gut microbiota, and eye movement.As observed in Fig. 9, we have provided a rough depiction of the prominent areas of biomarkers in the field of ASD.

4.2.1. Genetic biomarkers

ASD tends to aggregate within families, indicating a strong genetic component in its pathogenesis [38]. However, due to the diverse nature of the ASD population, pinpointing relevant gene mutations or variations remains a challenge. Over the past four decades, population-based twin and family studies have supplied compelling evidence that ASD constitutes a complex range of neurodevelopmental disorders. Its etiological model likely arises from specific genes and environments, with an added consideration of gene-environment interactions [39–41]. A meta-analysis of genome-wide associations has highlighted five significant loci influencing ASD risk [42]. Furthermore, this analysis revealed that candidate genes associated with ASD exhibit their highest expression levels during fetal corticogenesis. This observation reinforces the notion that both rare and common genetic variations linked to ASD impact gene expression during the development of the cerebral cortex [43]. Intriguingly, findings from Martin's research have indicated a hierarchical structure among layer 5 pyramidal neurons in the developmental stages of cerebral cortex. Risk gene mutations associated with ASD can disrupt the developmental traits of these neurons [44]. However, the question of whether ASD-related genetic variations primarily affect cortical development by interfering with the hierarchical and active characteristics of cortical neurons warrants further exploration.

Single-cell sequencing analysis has verified extensive transcriptomic changes throughout the cerebral cortex in individuals with ASD. This suggests that the brain alterations associated with autism are comprehensive across the entire cerebral cortex, extending beyond specific regions previously believed to impact social behavior and language [45]. Therefore, future analyses across multiple tissues should prioritize the representation of the broadest possible range of cortical regions.

It is equally important to assessing the regulatory role of epigenetics in the pathophysiology of ASD. Studies have quantified patterns of DNA methylation in ASD and identified several differentially methylated regions (DMRs) [46]. These DMRs tend to cluster in regions related to gene promoters, gene bodies, and the 3′ untranslated regions of a spectrum of ASD-related genes [47–49]. This underscores the association between aberrant DNA methylation and ASD. However, data on the specific number and location of DMRs in ASD remain limited. A meta-analysis has revealed abnormalities in core indices of cellular methylation capacity in the blood of ASD

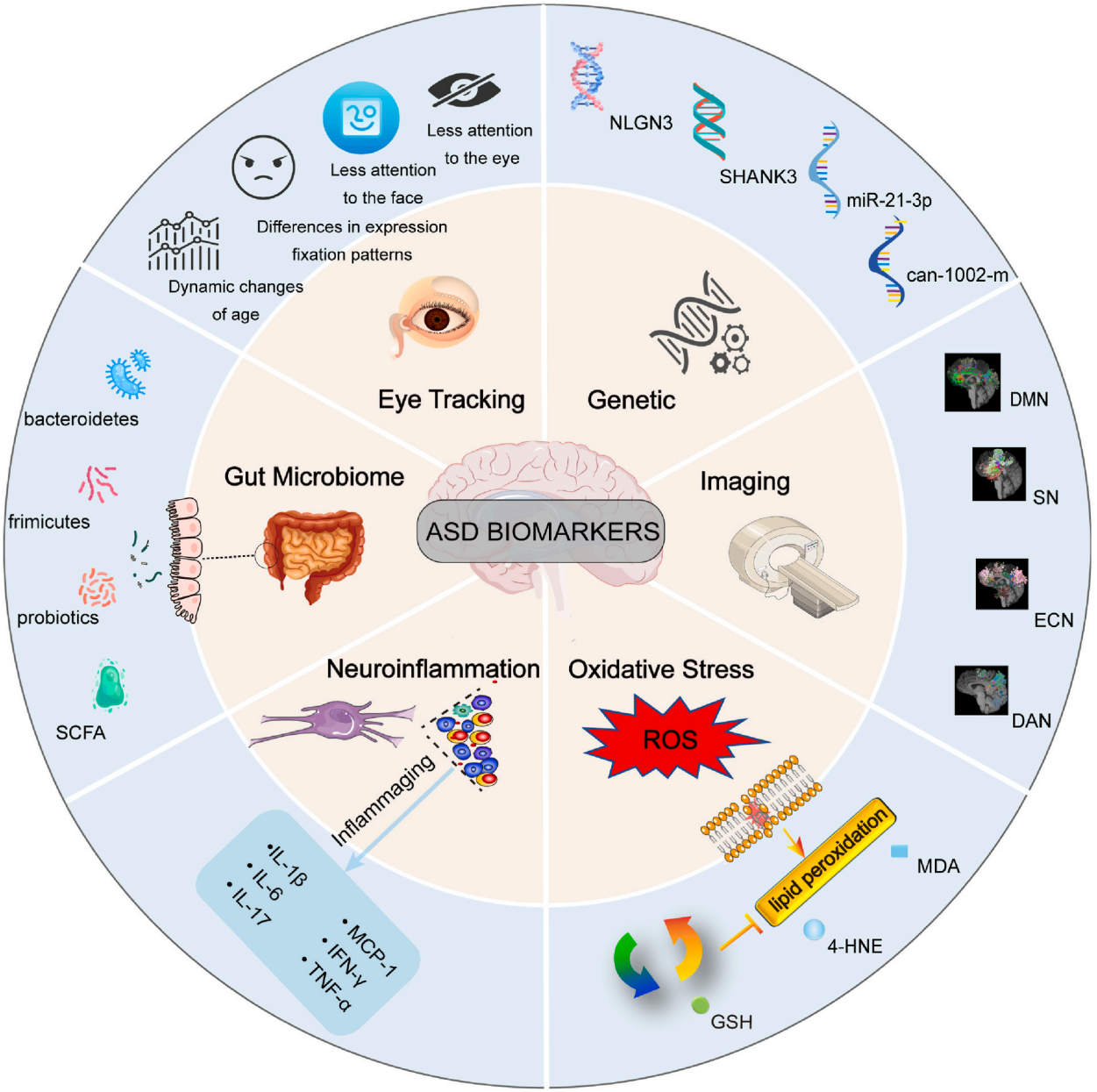

Fig. 9. Distribution of key biomarkers in hotspot areas of ASD biomarker research.

patients. This includes significantly reduced methionine and S-adenosylmethionine (SAM) levels, elevated SAM/S-adenosylhomocysteine (SAH) ratios, and increased SAH levels [50]. Further research of these aberrant indicators is essential due to their potential research value in developing biomarkers for early ASD diagnosis and treatment targets. Epigenetic dysregulation in ASD also involves posttranslational histone modification. An extensive histone acetylome-wide association study has identified a common acetylome signature shared by more than 68 % of syndromic and idiopathic ASD cases in the prefrontal and temporal cortex. This suggests a link between epigenetic modification processes and ASD, implying that epigenetics plays a role in regulating the ASD phenotype [51].

"Dark matter" regions of the genome, which do not directly encode proteins, have been proven invaluable in advancing biomarker research in ASD studies. They have also shed light on the role of non-coding RNAs (ncRNAs) in ASD pathophysiology. An analysis of whole-genome microRNA (miRNA) expression profiles has delineated the targets of several prime candidate miRNAs and perturbed co-regulatory modules in ASD [52]. This examination has unveiled the upregulation of hsa-miR-21-3p, which may lead to downregulation of neuronal and synaptic genes, correlating with neuronal and synaptic defects in ASD. Another primate-specific miRNA, has-can-1002-m, is downregulated in ASD; it regulates signaling pathways linked to neural stem cell proliferation, such as EGFR and

FGFR pathways. These mechanisms may reflect the neural development process of early postnatal brain overgrowth in ASD [52,53]. It is important to note, however, that this study primarily focused on brain tissue samples from adults, potentially missing early genetic perturbations that play a causal role.

4.2.1.1. Challenges and future perspective. Most studies attempting to identify genetic mutations and variations underlying ASD have struggled to replicate earlier findings or reproduce them in different cohorts [54]. The primary reason for this lack of replication is the considerable heterogeneity within ASD populations. To address this, researchers suggest categorizing ASD individuals into subgroups based on behavioral symptoms, comorbidities, or variations in metabolic and immune functions. This approach aims to reduce the heterogeneity within hereditary ASD cases [10,11]. Consequently, it is crucial to incorporate phenotypic identification into genetic and other biological analyses of ASD [55]. A cohort study has affirmed that incorporating phenotypic subgroups enhances the sensitivity and specificity of gene-related biomarker predictions [56]. Based on these insights, future ASD research should prioritize examining specific phenotypes to uncover ASD subgroup-specific genes, signalling pathways, and signaling pathways. This approach will mitigate the heterogeneity observed in genetic analyses and offer new prospects for diagnosis and treatment.

In addition to the substantial genetic heterogeneity, the extent to which the genetic risk for ASD is distinct from other neurodevelopmental disorders remains a subject of debate. Studies investigating copy number variations (CNVs) have revealed that the same genetic variation structure can lead to differing diagnostic outcomes, including but not limited to schizophrenia, attention deficit hyperactivity disorder, and epilepsy [57,58]. Despite the significant genetic heterogeneity in ASD, there is an overlap with certain neuropsychiatric disorders. However, it's undeniable that advancements in gene capture techniques and methodologies over the past decade, along with the resulting wealth of genetic discoveries, have played a pivotal role in unraveling the pathophysiology of ASD and contributing to enhanced clinical management. Future efforts should concentrate on further expanding foundational omics databases, spanning diverse age groups, genders, and species, with a focus on capturing individual ASD developmental trajectories.

Unlike genomics, the epigenome is modifiable. First, it remains uncertain whether altered epigenetic patterns actively drive ASD or whether it results from other pathogenic factors. Establishing a causal relationship is of paramount importance. Second, the use of numerous psychotropic drugs may influence the study of epigenetic genomes, potentially leading to biased results [59]. In epidemiological studies, controlling for the use of medications, individual developmental trajectories, age, and other covariates is necessary to establish a reliable causal connection between environmental exposures, maternal prenatal exposures, and the uterine epigenome. Exploring these aspects alongside genetic factors, including through methodologies such as Haplotype Analysis, will provide a more comprehensive understanding of ASD etiology and contribute to improved diagnosis and treatment strategies.

4.2.2. Imaging biomarkers

In studies on biomarkers for ASD, MRI has emerged as invaluable technology for identifying neurodevelopmental variations in brain anatomy, funtional, and connectivity underlying ASD. Alterations in functional connectivity have been garnered support as a link between regional brain activation and phenotypic presentation [53].

4.2.2.1. Structural imaging. Multiple longitudinal MRI studies have evaluated differences in cortical column metrics (such as volume, surface area, thickness, and folding) and white matter tract integrity throughout the lifespan. For instance, a prospective neuroimaging study involving infants at risk of ASD has demonstrated that children who later develop ASD exhibit an excessive expansion of cortical surface at 6–12 months, with a greater involvement of areas associated with auditory and visual processing [60]. Moreover, certain regions of the brain, including anomalies in Broca's area and Wernicke's area, have been linked to social communication and language deficits in ASD individuals [13,61]. Abnormalities in the frontal-temporal regions and the amygdala have been associated with impairments in social-emotional processing [62,63], while the frontal lobe cortex and the caudate nucleus (part of the fronto-striatal system) may mediate repetitive and stereotyped behaviors [14,64].A cohort study further identified structural alterations in the mesolimbic reward pathway, providing support for the hypothesis that compromised reward processing circuitry could contribute to social impairment in ASD individuals [65]. Notably, certain studies have discerned differences in brain structure when comparing patients with ASD with other patients having neurodevelopmental disorders such as schizophrenia and attention-deficit/hyperactivity disorder [66,67]. The significance of these structural imaging findings lies in their potential to aid in the diagnosis of patients with ASD who are challenging to classify solely based on clinical symptoms.

In summary, these longitudinal MRI study outcomes underscore the connection between ASD and brain structural variations, along with the potential association of specific brain regions' anomalies with distinct ASD symptomatology. These revelations contribute to a deeper comprehension of ASD's neurobiological underpinnings and offer prospective imaging groundwork for its early diagnosis.

4.2.2.2. Functional imaging. When discussing the research progress in ASD, resting-state fMRI plays a pivotal role in unraveling the neural characteristics of the ASD brain. This research methodology allows us to capture the functional connectivity and activity within the brain in the absence of specific tasks, thereby providing an in-depth insight into the neural mechanisms of ASD [68]. Within this domain, an increasing number of studies using resting-state fMRI have been focused on exploring the connectivity alterations within the brains of individuals with ASD. These studies have focused on various functional networks, such as the default mode [69–71], salience [72,73], central executive [73–75], and dorsal attention network [68,74,75]. In these networks, connectivity changes may manifest as either enhanced or attenuated, closely associated with core ASD symptoms such as social interaction deficits and impaired cognitive flexibility [68]. Furthermore, resting-state fMRI investigations have also examined connectivity changes between different brain regions, encompassing both homotopic and heterotopic interhemispheric connections [76,77]. In ASD patients, distorted

connectivity patterns within and between hemispheres have been observed, possibly linked to clinical features of autism and social communication impairments [77].

During the early developmental stages, certain studies have specifically delved into the resting-state functional connectivity of children and infants with ASD, revealing that even at an early age, atypical brain connectivity may exist [72,78]. Notably, some studies have discovered a correlation between the functional connectivity patterns in infancy and subsequent ASD diagnoses, particularly in high-risk populations [79]. Encouragingly, research has demonstrated that the analysis of resting-state fMRI data can be employed to predict the diagnosis of ASD during infancy. Utilizing machine learning algorithms, these studies successfully predicted ASD diagnoses with 100 % accuracy at 6 months of age by analyzing brain connectivity patterns associated with ASD [17]. This suggests that the patterns of brain connectivity may pre-exist before the manifestation of symptoms, potentially aiding in early-stage diagnosis and intervention for ASD.

4.2.2.3. Challenges and future perspective. In the context of ASD, the journey towards identifying imaging biomarkers has been marked by significant progress, while concurrently encountering specific challenges that are shaping the future trajectory of this field.

These challenges encompass the intrinsic heterogeneity of ASD, presenting a formidable hurdle in pinpointing universal biomarkers due to the diverse spectrum of clinical and cognitive features exhibited by individuals. Additionally, the requirement for substantial sample sizes, coupled with the need for sample diversity, poses difficulties in recruitment and data collection standardization, affecting the reliability of findings.Future endeavors in ASD imaging biomarker research should pivot around several focal points to propel its advancement.

Progress in ASD imaging biomarker research has unfolded critical trajectories. Firstly, rigorous scrutiny of cerebral structure and functional attributes patients with ASD becomes paramount to unearth refined imaging biomarkers. This endeavor mandates the strategic assimilation of contemporary data analytical methodologies, such as machine learning and artificial intelligence, to unveil latent malady-specific biomarkers. Secondly, in light of the burgeoned stride in precision medicine, forthcoming inquiries should judiciously explore the potential utility of these imaging biomarkers to prognosticate the responsiveness of patients with ASD to diverse therapeutic modalities. Through analysis of patient imaging data allows for the identification of salient features that correlate with treatment responses. Consequently, the application of personalized therapeutic strategies holds promise to optimize treatment efficacy and align interventions with the bespoke exigencies of individual patients' needs. Furthermore, the synergistic combination of distinct imaging modalities, including Structural Magnetic Resonance Imaging(sMRI), fMRI, and EEG, holds substantive promise in providing a comprehensive depiction of the intricate neurobiological underpinnings of ASD. By harmoniously integrating these multimodal datasets, a more comprehensive insight into the structural and functional dynamics of the ASD brain can be gleaned, thereby fostering a more precise delineation of imaging biomarkers.

In anticipation of forthcoming research, longitudinal studies assume an indispensable facet. The longitudinal documentation and observation of the evolving structural and functional metamorphoses within the brains of patients with ASD facilitate a nuanced comprehension of the developmental trajectory of the disorder. This longitudinal perspective augments our comprehension of the disease's evolution and expedites the dynamic refinement and validation of imaging biomarkers over temporal continuums.

4.2.3. Oxidative stress biomarkers

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's defense mechanisms orchestrated by antioxidants [80]. This equilibrium disruption leads to inadequately controlled excessive ROS, which can potentially trigger various pathological changes, including damage to lipid membranes, proteins, DNA, and disruptions in mitochondrial function [81]. In the context of ASD, children appear to be more vulnerable to oxidative stress, evidenced by escalated lipid peroxidation due to increased free radical generation and insufficient antioxidant protection [82–84], especially during critical stages of brain development [85]. Individuals diagnosed with ASD display physiological abnormalities linked to oxidative stress, such as heightened lipid peroxidation products [86,87] and reduced glutathione reserve capacity [88,89], particularly in brain tissue. These anomalies tend to localize within brain regions associated with speech and auditory processing, social behavior, memory, and sensory-motor coordination [84,90].

Lipid peroxidation plays a pivotal role in oxidative stress, involving the process in which oxidants target lipids containing carbon-carbon double bonds, leading to oxidative modifications in cellular membranes [91]. Consequently, byproducts like malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), and F2-isoprostane emerge as potential biomarkers reflecting oxidative stress status and associated disorders in vivo [92]. MDA has been implicated in initiating cellular stress and apoptosis under carbonyl stress, thereby potentially compromising brain function [93], which could contribute to autistic behaviors in individuals with ASD [94]. Several studies utilizing the thiobarbituric acid reactive substances assay consistently reveal significantly elevated plasma MDA levels in patients with ASD compared to age-matched healthy counterparts, with a positive correlation to ASD severity [95–97]. This underscores the predictive and evaluative value of plasma MDA in assessing ASD risk and therapeutic efficacy [98]. However, a different study suggested that changes in plasma MDA levels were not associated with ASD [99], possibly due to the presence of the blood–brain barrier and the low concentration of blood markers. In instances of limited detection method sensitivity, trace MDA levels in peripheral blood might not be quantified adequately. Improving detection methodologies, such as using more sensitive and specific chromatography–mass spectrometry (LC-MS) and gas chromatography–mass spectrometry (GC-MS) [100–102], could be effective. Furthermore, considering that various neurodevelopmental disorders related to cognitive and behavioral impairments correlate with heightened MDA [103,104], combining plasma MDA with other specific indicators for ASD diagnosis is advisable.

In conjunction with MDA, other significant lipid peroxidation markers, like 4-HNE and F2-isoprostane [105], hold substantial

research value. Studies suggest their potential involvement in ASD pathogenesis [106,107]. The effects of 4-HNE might stem from endoplasmic reticulum (ER) stress in the human autistic brain [106], while F2-isoprostane could result from platelet and vascular activation [107]. Numerous investigations have identified elevated levels of 4-HNE [108] and F2-isoprostane [109–111] in blood samples from children with ASD. A surge in gastrointestinal (GI) symptoms in children with ASD, linked to mitochondrial redox imbalances in their intestinal environment, has been previously documented [112,113]. In a substantial case-control study, elevated plasma F2t-isoprostane levels were found to be strongly correlated with ASD accompanied by GI dysfunction [114]. This supports the potential utility of F2t-isoprostane in predicting GI symptom risk and monitoring therapeutic outcomes in ASD patients.

Glutathione, the brain's predominant endogenous antioxidant, plays a pivotal role in cell signaling and antioxidant defense [115,116]. Disruptions in glutathione metabolism might arise from congenital neuroinflammatory shifts [117] and imbalances in intestinal microflora [118], contributing to the pathophysiological understanding of ASD. Genetic variations within glutathione-related metabolic pathways have been substantiated [119–121], correlating with behavior in individuals with autism [122,123]. Children diagnosed with ASD exhibit a decrease in reduced glutathione (GSH) concentration and an increase in oxidized glutathione (GSSG) levels compared to age-matched controls [124–127]. However, these findings remain contentious across different research groups [128]. Notably, consistent results emerge concerning the GSH/GSSG redox ratio. Multiple studies indicate a 2–3 times decrease in GSH/GSSG redox ratios in the blood [124,127,129–131], brain tissue [89], and lymphoblastic cells [132] of patients with ASD patients compared to controls, reflecting parallel changes between the central and peripheral nervous systems. The study of ASD brain tissue also revealed a correlation between a low GSH/GSSG redox ratio and the inhibition of redox-sensitive mitochondrial enzymes [89]. In conclusion, the GSH/GSSG redox ratio emerges as a dependable ASD biomarker with high sensitivity and repeatability.

Furthermore, alterations in the activities of antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT), have been observed in individuals with ASD [133]. These observations suggest a potential disruption in the balance of the antioxidant defense system of individuals with ASD. Diminished antioxidant enzyme activities are implicated in patients with ASD, rendering cells less capable of effectively combating oxidative stress [134]. Nevertheless, by enhancing the functionality of the antioxidant enzyme system, it is plausible to mitigate the oxidative stress damage experienced by these patients, thereby potentially ameliorating their pathological conditions [84,133]. This theoretical framework advocates for the concept of bolstering cellular antioxidant capacity as a strategy for treating ASD, offering promising leads for the development of novel therapeutic approaches. It is important to note that these hypotheses necessitate further research to ascertain their practical efficacy and applicability in clinical settings.

4.2.3.1. Challenges and future perspective. While brain tissue or cerebrospinal fluid (CSF) samples can directly detect oxidative stress in the brain, the complexity of detection methods and risks associated with the sampling process primarily confine this approach to scientific research, with limited application in clinical practice. In contrast, peripheral biofluid samples offer non-invasiveness, ease of collection, and repeatability, making them a preferable choice for research. However, the current repertoire of biomarkers in peripheral biofluids does not allow for an accurate identification of brain or peripheral oxidative stress [135]. Nevertheless, the rapid advancement of metabolomics technology holds promise for addressing this challenge. Metabolomics in ASD research seems likely to enable the identification of metabolites closely associated with oxidative stress, thereby facilitating a more comprehensive understanding of the biological status of patients with ASD [136,137]. Various targeted metabolomics techniques have been developed and utilized to measure oxidative stress biomarkers with precision [138,139], such as homocysteine, methionine, and vitamins B6, B12, and B9, revealing their correlations with ASD [135]. Furthermore, by integrating metabolomics data with other omics data (such as genomics and proteomics), we can discern metabolites linked to oxidative stress, changes in protein expression, and genetic variations, thereby achieving a more comprehensive grasp of the molecular mechanisms underpinning ASD pathogenesis [140,141]. Nevertheless, future research needs to confront certain challenges. Exploring additional biomarkers in peripheral biofluid samples, like brain-derived neurotrophic factor (BDNF) [142] or brain-derived exosomes [143], promises to yield more comprehensive insights. Additionally, metabolomics technology faces limitations in sample stability, standardization, and data interpretation, necessitating ongoing technological innovation and method refinement. The advancement of tools such as bioinformatics and artificial intelligence will elevate the capacity to handle extensive multi-omics data, consequently expediting the discovery and validation of biomarkers [144].

4.2.4. Neuroinflammation biomarkers

In recent years, research has indicated that genes associated with the risk of ASD, identified within the cortical tissue organization, are enriched in categories related to immunity and inflammation [145]. This lends support to the connection between the immune system, neuroinflammatory events, and ASD. Nonetheless, it remains unclear whether neuroinflammation acts as a causative factor of ASD or whether it is a downstream reaction to other biological processes, such as oxidative stress. Studies have revealed activation and increased density of microglial cells in the ASD brain parenchyma, suggesting a correlation with abnormal functional connectivity among regions of the ASD brain [146,147].

Animal model research has revealed that maternal inflammation is a risk factor for ASD. Activation of the maternal immune system during pregnancy leads to offspring exhibiting behaviors resembling ASD and alterations in immune cell function [148]. The interaction between immune cells is often regulated by cytokines, which are used as biomarkers to assess immune dysregulation and pro-inflammatory states in ASD. Meta-analyses of pro-inflammatory cytokines in ASD consistently reveal elevated levels of factors such as IFN-γ, IL-1β, IL-6, and TNF-α when compared to control groups [149].

Chemokines play a crucial role in guiding immune cell chemotaxis and recruitment to sites of inflammation. Elevated

concentrations of various chemokines associated with congenital immune activation, including MCP-1, RANTES, eotaxin, IL-8, and CXCL1, have been observed in pediatric ASD [150,151]. Furthermore, some studies have suggested a correlation between elevated MCP-1 levels in maternal amniotic fluid and an increased risk of ASD in offspring [152]. Concentrations of chemokines like MIP-1α, MIP-1β, and IP-10 have also been associated with social behavioral impairments [153], implying the impact of chemokines on the chemotaxis and migration of monocytes/macrophages during ASD diagnosis, at birth, and even during pregnancy.

4.2.4.1. Challenges and future perspective. Despite the majority of ASD studies confirming increased levels of inflammatory cytokines and chemokines, results are not always consistent. Contradictory findings could stem from differences in patient and control populations, sample types and processing, as well as the use of diverse immunological analyses and techniques. Additionally, variability in biomarkers is present within the normal population, making it essential to establish reliable criteria for distinguishing patients with ASD from healthy individuals. This complexity also makes it challenging for a single biomarker to serve as a specific diagnostic tool for ASD.

Future research directions might involve more multicentre studies to enhance sample representation and further validate the stability and reliability of biomarkers. Integrating neuroinflammation-related biomarkers with clinical symptoms, genetic backgrounds, and environmental factors could aid in establishing more accurate ASD diagnostic tools. Moreover, a comprehensive approach integrating information from multiple biomarkers could enhance the understanding of the intricate etiological mechanisms of ASD. Delving deeper into the role of the immune system in neural development could unveil more nuanced correlations with ASD, offering more precise avenues for early diagnosis and treatment strategies.

4.2.5. Gut microbiota biomarkers

In recent years, the relationship between ASD and the gut microbiota has become a prominent area of research. Studies have indicated that there exists a dysregulation in the composition of gut microbiota in patients with ASD, primarily manifested by alterations in the relative abundances of certain bacterial groups [154]. Specifically, a meta-analysis of the gut microbiota in children with ASD revealed a significant increase in the relative abundance of the Bacteroidetes phylum (such as Bacteroides and Parabacteroides genera) as well as the Firmicutes phylum (especially Clostridium, Faecalibacterium, and Phascolarctobacterium genera). Conversely, the relative abundances of beneficial bacteria such as the Coprococcus and Bifidobacterium genera were found to be lower [155]. However, this conclusion is still debated within the academic community. One study has suggested the presence of overgrowth of Proteobacteria in the ASD gut, with their relative abundance linked to allergic symptoms [156]. Furthermore, research has identified specific microbial communities, notably within the Bacteroides family and Lachnospiraceae, where reduced microbial quantities correlate with neurodevelopmental levels and behavioural symptoms like social impairment in patients with ASD [157]. This highlights the potential role of microbial activity and their metabolic products in the development and severity of ASD. Notably, investigations have revealed similarities in gut microbiota composition between children with ASD and their mothers, implying that maternal influence via microbial transmission could impact the microbiota of children with ASD and consequently influence ASD development [158]. However, it is essential to emphasize that while these research findings provide valuable insights into the relationship between ASD and gut microbiota, further studies are necessary to elucidate the mechanisms and implications of these discoveries.

The activity of the gut microbiota generates various metabolites, including short-chain fatty acids (SCFAs) and amino acids. These metabolites play a crucial role in regulating brain function. Research indicates that SCFAs can cross the blood-brain barrier and influence early brain development by modulating the synthesis of neurotransmitters such as serotonin and dopamine [159].Specifically, SCFAs are a group of compounds produced by intestinal bacteria during the fermentation process, with one of the key components being propionic acid [160]. Of particular interest, research has revealed a significant reduction in the total amount of SCFAs and a corresponding increase in propionic acid concentrations in children with ASD [160,161]. This alteration in SCFA levels may be associated with the progression of ASD symptoms, and this notion has been supported by animal model experiments further support this notion. Injecting propionate into the lateral ventricle of the brain leads to behaviors and physiological changes resembling those of autism [161]. These alterations may involve delays in neural development and the occurrence of epilepsy [162], further underscoring the profound impact of gut microbiota metabolites on brain function.

Furthermore, research has unveiled a close relationship between the gut microbiota and neurotransmitters, a field referred to as the "Gu–Brain Axis" [163]. Certain protective bacteria, such as those from the Bifidobacterium and Lactobacillus genera, have the capacity to produce the primary inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [164], which is intimately linked to the brain's excitatory neurotransmitter, glutamate [165]. Building upon the hypothesis of an "Excitation/Inhibition (E/I) Imbalance," it is posited that an imbalance between excitatory (primarily mediated by glutamatergic neurons) and inhibitory (primarily mediated by gamma-aminobutyric acid-ergic neurons) mechanisms forms the foundation for behavioral characteristics such as anxiety and social behavioral disturbances in individuals with ASD [166]. This E/I imbalance is likely to be intricately connected with the composition and functionality of the gut microbiota. Studies indicate that specific gut microbiota can influence brain activity by modulating neurotransmitter levels, particularly those producing GABA, which could influence inhibitory neural transmission by regulating GABA levels [164,167]. Consequently, disruptions in the gut microbiota could lead to disturbances in neurotransmitter levels, potentially triggering or exacerbating E/I imbalances in individuals with ASD, thereby affecting behavior and emotions. This underscores the vital role of the gut microbiota and neurotransmitters in the pathogenesis of ASD [168].

4.2.5.1. Challenges and future perspective. While observed changes in gut microbiota related to ASD have been reported in the

literature, the study of mechanisms by which these alterations influence brain function and behavior remain unclear. Moreover, the gut microbiota is subject to modulation by various factors such as diet, genetics, medication, and environment, exhibiting a significant degree of inter-individual variability. This variability poses a challenge in identifying stable microbial features associated with ASD. To address this challenge, several strategies can be employed: Firstly, conducting long-term longitudinal studies that include patients with ASD and tracing the development of gut microbiota from childhood to adulthood, would aid in revealing patterns of microbial variation and how these changes correlate with the evolution of ASD symptoms. Secondly, integrating multi-omics data layers, including metagenomics, metatranscriptomics, and metabolomics, would provide a more comprehensive understanding of the interplay between gut microbiota, host physiology, and pathways related to ASD. Additionally, leveraging of microbial compositional features would facilitate the development of personalized therapeutic interventions, enabling more precise ASD interventions while accounting for individual differences and the diversity of gut microbiota composition.

4.2.6. Eye tracking biomarkers

Eye movement biomarkers refers to a method of identifying potential indicators of ASD by observing and analyzing individuals' eye movement patterns while they view, fixate on, and track visual stimuli. Numerous studies have indicated differences in visual attention between individuals with ASD and those with TD [16,169], and those differences are closely correlated with the social impairments characteristic of ASD [170–172]. In terms of gaze patterns, individuals with ASD tend to focus more on non-facial areas, such as the mouth, ears, or background, and less on the eye region [173]. Furthermore, the duration of eye contact is positively correlated with social skills and sensitivity to emotion perception. Research has also discovered that reduced visual attention to the eye region is associated with more severe social impairments in adults with ASD [174]. This phenomenon may stem from reduced social significance perception of the eye region among individuals with ASD, potentially impacting their ability to extract emotional information from facial expressions.Additionally, patients with ASD may exhibit distinct gaze patterns when observing different emotional expressions. Evidence suggests that when viewing fearful faces, individuals within the autism spectrum may display heightened activity in key areas of the social brain, while reduced activity may be observed when observing happy faces [175]. These varying neural response patterns could contribute to the integration of theories related to arousal and social motivation in ASD, thereby enhancing our comprehension of the neurobiological underpinnings of ASD [176]. Indeed, the fixation patterns of ASD patients may undergo changes across different age stages [18] possibly reflecting developmental delays or asynchrony in emotional cognition and social skills.

4.2.6.1. Challenges and future perspective. Nevertheless, eye movement biomarker research in ASD still faces numerous challenges. A primary challenge is the lack of standardized research methods and experimental protocols, leading to poor comparability between different studies and low reproducibility of results, thereby diminishing the reliability and replicability of research outcomes [15]. Additionally, factors such as varying experimental setups, ambient lighting, and participant positioning can influence the collection of eye movement data, resulting in substantial variability between outcomes and hindering the establishment of consistent patterns. To enhance research reproducibility, future studies need to establish unified eye movement research methodologies and experimental protocols, alongside the sharing of validated stimulus materials. The formulation of these standards and protocols would help reduce methodological discrepancies and enhance result consistency. Furthermore, the integration of eye movement data with other neurobiological data sources (i.e. machine learning, electroencephalography, and functional magnetic resonance imaging) can offer a more comprehensive perspective, facilitating a deeper understanding of cognitive and perceptual processes in response to stimuli in patients with ASD [177]. According to a meta-analysis combining eye tracking technology with machine learning, machine learning models based on eye movement data achieved a classification accuracy of 81 % in distinguishing individuals with ASD from those with TD, with a sensitivity of 84 % and specificity of 79 %. Subgroup analysis further revealed accuracy rates of 88 %, 79 %, and 71 % for preschool children, school-aged children, and adolescents to adults, respectively. These findings underscore the potential value of combining eye tracking technology with machine learning for early ASD diagnosis [178]. Finally, ASD often co-occurs with other comorbid symptoms such as social anxiety and ADHD. These comorbid symptoms can impact emotion recognition and eye movement patterns, intensifying the complexity of research outcomes. Future research needs to better account for these comorbid symptoms to more accurately comprehend the differences in emotion recognition and eye movement within ASD. In conclusion, despite the challenges, the integration of diverse technical approaches remains a crucial avenue for further exploration and understanding of eye movement biomarkers in ASD.

4.2.7. Integration of biomarker modalities

The integration of genetics and neuroimaging aims to precisely localize gene effects relevant to the brain, identifying convergences between molecular-level impacts, circuit-level structure, and function across multiple risk genes. A systematic review of structural MRI findings in monogenic ASD underscores that approximately 51.7 % of individuals harboring significant genetic variations linked to ASD manifest brain abnormalities, particularly salient among pediatric patients [179,180]. The affected neuroanatomical domains predominantly encompass white matter, gray matter, and ventricles/cerebrospinal fluid regions, with white matter anomalies exhibiting particular prominence. This underscores the presence of disruptions in connectivity [181,182]and myelination development [182–184] in children with ASD. In the realm of functional imaging, consistent correlations are observed between the depletion of ASD risk genes Shank3 [185] and cntnap2 [186] and alterations in prefrontal functional connectivity. Notably, these deletions are associated with deficits in social interaction and communication behaviors, thereby contributing to the pathogenesis of ASD [185]. These findings illuminate the pivotal role of prefrontal connectivity disruptions within the context of ASD risk gene mutations, offering insights into the intricate neurobiological underpinnings of the disorder.

Machine learning, situated at the intersection of neuroimaging and genetics within the realm of artificial intelligence, has served as a catalyst for pioneering advancements in ASD diagnosis [187]. Recent research underscores the distinct advantages of AI-powered medical devices for ASD diagnosis, renowned for their precision, adept data fusion, and optimal resource utilization [19]. Harnessing genes such as ARSD, MAGEB16, and MXRA5, deep learning models enhance conventional methods, elevating ASD screening accuracy by approximately 13 % [188]. In a separate investigation, employing machine learning techniques, scrutinization of brain imaging data from 252 subjects, including typically developing individuals and those with ASD, achieves an impressive 91 % accuracy in ASD diagnosis. This research underscores the paramount significance of functional connectivity attributes in ASD studies, revealing robust correlations between aberrations in somatosensory, default mode, and visual brain regions, and manifestations of ASD [189]. Proposing an alternative approach, another study introduces a multi-site adaptation framework utilizing functional MRI data. Employing low-rank representation decomposition to mitigate data heterogeneity, it exhibits remarkable proficiency in ASD recognition [12]. In parallel, an international challenge disseminates MRI data sourced from over 2000 participants, unveiling the pronounced impact of functional MRI on prognosis relative to anatomical MRI. As sample sizes incrementally amplify, prediction accuracy stabilizes, albeit a vigilant stance against overfitting risks remains imperative. Notably, the study successfully forecasts external sample ASD diagnoses post-challenge, albeit with slightly diminished accuracy, underscoring the intricacies of data transfer [190].

When investigating into ASD biomarkers, the amalgamation of EEG and eye tracking data provides comprehensive insights. The integration of eye tracking and EEG frequency band power explores cognitive processing demands during text-image learning. Varied conditions allowing or restricting text-image integration unveil the interrelation between cognitive processing demands and integration circumstances. Furthermore, EEG alpha and theta frequency band power data support eye tracking outcomes [191]. Leveraging eye tracking and EEG recordings, it's evident that the ASD group manifests significantly diminished neural responses to facial stimuli, accentuating the utility of frequency-tagged EEG as a swift, objective, and dependable approach to monitor the decline in social preference [192]. Moreover, by employing a deep fusion approach that combines EEG and eye tracking data, a remarkable 95 % accuracy rate in distinguishing ASD from typically developing children was achieved, revealing robust correlations between EEG and eye tracking signals, particularly in terms of facial-related/joint attention covariance [193].

The novelty of this study lies in its utilization of bibliometric methods to gain a fresh perspective on ASD biomarker research. By deeply exploring the WOSCC database, the objective is to uncover collaborative research patterns, recognize influential scholars, and outline future research directions. This quantitative approach provides profound insights into the substantial progress in the ASD biomarker field, accentuates existing challenges, and proposes innovative research recommendations to address these challenges. Furthermore, this study delves into the integration of various biomarker modalities for a precise assessment of ASD features, positioning it at the forefront of the field.

Despite the study's merits, certain challenges were encountered during the methodology. Firstly, the data was exclusively extracted from the WoSCC database due to limitations in visualization software for merging databases. This limitation suggests that other databases such as PubMed, Scopus, and EMBASE may contain more comprehensive and influential literature records, thereby offering potential enhancements for future research efforts. Secondly, as of 2023, the year had not yet concluded, meaning that complete data for that year could not be included, introducing the possibility of research bias. Additionally, it is crucial to note that while the study relies on bibliometric data for quantitative analysis, it does not provide qualitative assessments of the clinical or practical significance of the research findings.

5. Conclusion

This study employs bibliometric methods to comprehensively investigate the field of ASD biomarkers, encompassing international collaboration trends, publication outputs, research hotspots, and future directions. Moreover, it underscores the significance of integrating diverse biomarker modalities, including genetics, neuroimaging, EEG, and eye tracking, for the precise assessment of ASD features. These findings provide a focused roadmap for future ASD biomarker research. Future research endeavors should center around the following areas:(1)Stratifying individuals with ASD into distinct subgroups based on behavioral symptoms, comorbidities, or metabolic and immune anomalies will aid in discerning unique pathogenic mechanisms within each subgroup.(2)The establishment of standardized research methodologies, bolstered by the power of large-scale "omics" technologies, is essential to enhance result reproducibility.(3)Through interdisciplinary collaboration and leveraging artificial intelligence and machine learning, amalgamating various biomarker modalities will enable a more precise evaluation of ASD.(4)Long-term tracking and longitudinal studies of ASD patients will provide deeper insights into the developmental trajectories of ASD and the temporal dynamics of biomarkers. These research directions promise to deepen our understanding of ASD, enhance the accuracy of early diagnosis, and offer greater possibilities for precision treatments. By integrating multidisciplinary approaches, harnessing advanced technologies, and leveraging extensive data analysis, ASD biomarker research is poised to reach new heights in the pursuit of improved ASD diagnosis and management.

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Ethics statement

Not Applicable.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Xinyue Xie: Writing – original draft. **Rongyi Zhou:** Writing – review & editing, Funding acquisition. **Zihan Fang:** Data curation. **Yongting Zhang:** Data curation. **Qirong Wang:** Visualization. **Xiaomian Liu:** Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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