• Bibliometric Research •

Bibliometric analysis of microphthalmos and anophthalmos over 20 years: from 2004 to 2023

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Abstract

● **AIM:** To conduct a bibliometric analysis of studies on microphthalmos and anophthalmos (M/A), explore research hotspots, and provide information on future research interests in this field to benefit clinicians and researchers.

● **METHODS:** Totally 751 publications related to M/A from the year 2004 to 2023 were collected from the Web of Science Core Collection database. These publications consist of both original and review articles, that are composed in English. The contributions of different countries, institutions, journals, and authors were analyzed, and network analysis was conducted by using Microsoft Excel 2021, VOSviewer, and R Studio to visualize research hotspots.

● **RESULTS:** Among all publications included, the highest number of publications came from USA (218, 29.03%). China followed with 99 publications (13.18%), and England with 86 publications (11.45%). The publications from the USA had the highest frequency of citations, with 16 699 citations, and the highest H-index of 49. The *American Journal of Medical Genetics Part A* (43, 5.73%) published the largest number of papers, and the University of London had the most publications (41, 5.46%). The genetic and molecular mechanisms of M/A were still unclear and the clinical intervention for M/A had gained a lot of attention as an emerging area of interest.

● **CONCLUSION:** Data have been gathered on the yearly count of published materials and citations, as well as the rise in publication trends, the efficiency of regions or countries, authors, journals, and organizations, along with the high-cited publications in M/A. The recent trend of research has shifted from genetic mechanisms to different clinical phenotypes and corresponding clinical interventions, which can give direction to future research.

● **KEYWORDS:** bibliometric analysis; network analysis; microphthalmos; anophthalmos

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INTRODUCTION

Microphthalmos is a congenital or developmental anomaly in which the eyeballs are abnormally small, caused by various factors. Anophthalmos is a condition in which patients are found to be born with a complete absence of the orbital eyeball and only the appendages of the eyes remain. Radiographic examinations are required for the diagnosis of anophthalmos[1]. Anophthalmos and microphthalmos (M/A) can be unilateral or bilateral and account for approximately 3%–12% of visual impairment in children[2-3], and up to 20% when including coloboma[4].

Microphthalmos can be categorized into three types: simple, complex, and colobomatous microphthalmos[5-6]. Simple microphthalmos is characterized by severe visual developmental disorders, but is anatomically intact; complex microphthalmos presents with a variety of ocular structural abnormalities; and colobomatous microphthalmos, also known as blind microphthalmos, is an irreversible blinding ophthalmopathy with no visual function[7-9]. In addition, it is generally recognized that the development of orbital structures is positively correlated with orbital development, and orbital development requires the stimulatory effect of the eyeball[10-11]. Inadequate or absent orbital content that occurs during orbital development can lead to orbital-facial asymmetry or even severe deformity in children, which can have a huge impact

on the patient's mental health and quality of life[12-14]. At the same time, the reconstruction of facial appearance also causes a huge economic burden to the patient's family. What's more, M/A often occurs as a syndrome, accompanied by other systemic abnormalities[15]. Therefore, effective screening, rational assessment, and timely intervention for children with M/A during the developmental period have special clinical, psychological, and social significance[13,16]. Thus, we need to further enhance the management of patients with M/A[17].

Alteration of the genetic material is the most important cause of abnormal eye development in children with M/A, which can be categorized as chromosomal and genetic abnormalities[13,18-20]. Environmental factors are secondary, including infections during pregnancy, exposure to toxic and harmful substances, drug use, and smoking in early pregnancy[21-22]. However, the specific biological mechanism that leads to M/A is still not fully understood, and there is still no cause-specific treatment[1,3,23]. Thus, further research is needed to explore the pathogenesis of M/A and effective treatments. Existing interventions focus on improving the appearance of children and stimulating orbital development[24-25]. To ensure that the implant meets the needs of actual growth and development of the eyeball, a scientific assessment of the development of orbital soft tissues and bones in patients with M/A is required[26-27]. However, due to the low morbidity of M/A and the lack of large-sample studies, preoperative and postoperative outcomes of rehabilitation for M/A can only be assessed qualitatively and the results are not yet uniform. It is necessary to create screening tools that are based on evidence and can be used to determine assessment criteria for children with M/A[13,22].

Bibliometrics is a method of evaluating academic productivity and identifying research trends in a particular field. This involves both qualitative and quantitative analysis[28]. One application of bibliometric research is to examine research activity trends within a certain field, by looking at factors like region, journal, institution, scholar distribution, and hotspots, thereby assisting clinical decision-making and research trends[29-30]. There are currently various studies being conducted on M/A. During the first decade of the 21st century, research on M/A primarily concentrated on genetic mechanisms, while in the recent 10y, clinical manifestations of disease and intervention measures have gradually begun to receive attention[31-32]. However, to our knowledge, there are no bibliometric studies on M/A. Therefore, an urgent need for a thorough examination of the current literature on M/A exists. Since the pathogenesis of M/A is still unclear, relevant research is urgently needed. The objective of this study is to conduct an extensive analysis of the research trends related to M/A and identify its potential areas of research focus by employing bibliometrics and network analysis using the Web of Science Core Collection (WoSCC) database. This research study offers valuable insights into potential areas for future research and unexplored topics that can be beneficial for both clinicians and researchers. The research includes reviews and original articles that are written in English. Then, we aim to analyze and compare the contributions made by various countries, institutions, journals, and authors. Additionally, the study also highlights research hotspots that can be visualized and analyzed using network analysis techniques.

MATERIALS AND METHODS

Data Sources and Search Strategy For this research, a bibliometric analysis was carried out using the Science Citation Index Expanded (SCI-EXPANDED) of the Web of Science database. To collect data for our study, we utilized a specific search strategy within the core database of WoSCC. The strategy was as follows: TI(Title)=(microphthalmia OR anophthalmia OR microphthalmos OR anophthalmos OR Coloboma OR nanophthalmos OR nanophthalmia). We chose the keywords from the MeSH database and discovered a total of 2643 publications. To further refine the results, the duration was from "2004.01.01 to 2023.12.31". After conducting a thorough search, we excluded 344 publications that did not meet our criteria of being original articles or review articles. Subsequently, we filtered the remaining publications based on language, selecting only those written in English. This resulted in 985 publications being included for further analysis, as shown in Figure 1. To ensure the accuracy of our search results, two reviewers independently assessed the relevance of these manuscripts to M/A (Figure 1). We included studies on congenital microphthalmia and congenital anophthalmia. Our search strategy would have retrieved patients with anophthalmia who underwent enucleation due to trauma, tumors, or other factors. We excluded these publications. In addition, although we only retained original articles and reviews in our search strategy, some other types of articles, such as case reports, still appeared, and we also excluded these articles. We tried to resolve disagreements by establishing a clear searching strategy, independently screening publications, and using structured discussions. Finally, we got 751 publications and relevant information, such as abstracts, keywords, publication dates, authors, countries and institutions, H-index values, and other required items.

Analysis Tool The data from the publications provided were visualized using Microsoft Excel 2021 (Redmond, USA), VOSviewer (Leiden University, the Netherlands), and R studio (version 4.1.3). The proportion of publications in a particular field compared to all fields in the WoSCC database was defined as the relative research interest (RRI). The analysis involved examining how the number of publications and RRI changed over time. Additionally, citation reports, impact

factor (IF), and H-index were obtained from the WoSCC and imported into Microsoft Excel 2021 for further analysis. These can demonstrate the impact of the publications and research, which were displayed according to the research of countries/regions and annual publications. Publication growth trends of the top four countries/regions with the most publications were analyzed and visualized by Microsoft Excel 2021, which were generated with a fitting model: $f(x)=ax^3+bx^2+cx+d$. The top 20 counties and affiliations with the most publications, the top 10 authors with the most publications, and the top 10 papers with the most publications were shown in figures and tables, respectively. The keywords were classified into various clusters based on the average appearance year by VOSviewer and the keywords were color-coded accordingly. Besides, the research trend of the past 20y was described and visualized *via* R Studio and bibliometrix package.

RESULTS

Annual Number and Distribution of Publications The inclusion criteria were met by a total of 751 publications. According to Figure 2A, the USA was responsible for the highest number of publications (218, 29.03%) between the years 2004 and 2023, followed by China (99, 13.18%) and England (86, 11.45%). During the past 20y, the total number of publications worldwide showed a stable trend, with the most publications in 2020. Between 2004 and 2020, except for 2013, the USA ranked first according to the annual publications in this field. China had its first publication in this field in 2006. Since 2012, publications from Chinese researchers in this field have grown at an alarming rate. China has had the most annual publications since 2021. Between 2014 and 2022, there was a downward trend observed in RRI, which used to fluctuate between 0.002% and 0.003% before 2014 (Figure 2A).

Distribution of Co-citations and H-index From 2003 onwards, a total of 16 699 citations have been recorded for all M/A-related publications, not including 13 605 self-references. On average, each publication has received 22.23 citations. Publications from the USA were referred to more frequently than those from other nations, receiving 7743 citations and 7338 non-self-citations, and achieving the highest H-index of 49. China ranked second in total publications, but lagged behind in the number of citations and H-index. It had 876 citations (805 non-self-citations) and the H-index ranked 7th (H-index=17). England ranked second in both citations and H-index, with 3543 citations (3493 non-self citations) and an H-index of 31 (Figure 2B).

Distribution of Growth Trends in Publications The growth of publications in the field of M/A was demonstrated through fitting curves and a positive correlation was observed between the annual global number of publications and time (Figure 3). Based on this model, predictions for publication trends in the upcoming years can be made. Our findings suggest that there has been a gradual increase in global publications. The USA

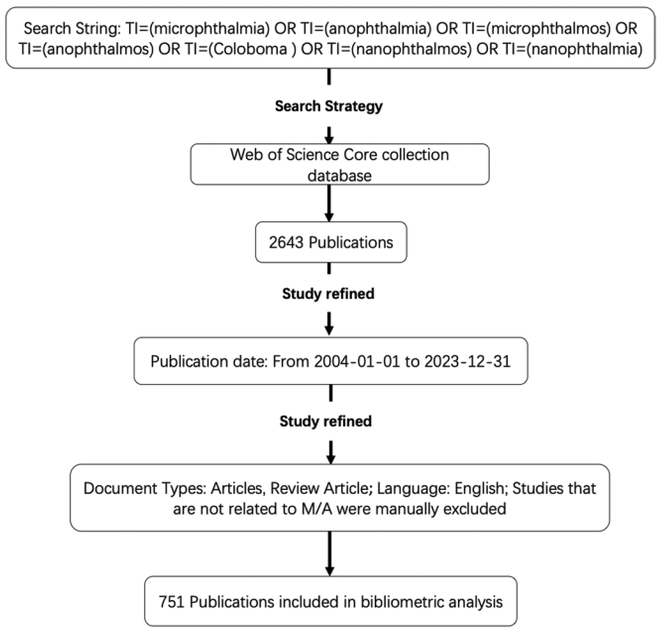

Figure 1 The process of searching and screening publications related to microphthalmos and anophthalmos in the Web of Science database.

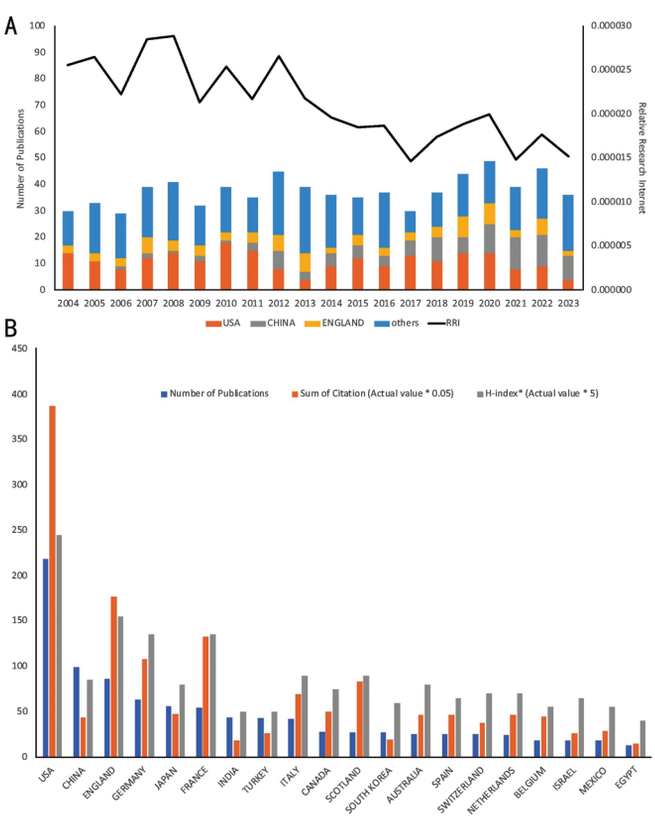

Figure 2 Research efforts on microphthalmos and anophthalmos in various countries and regions A: The histogram displays the annual count of publications along with the count of publications from the three leading countries and regions. In the line chart, the variation in relative research interest is demonstrated. B: Publications, citations (×0.05), and H-index (×5) of the top 20 countries or regions.

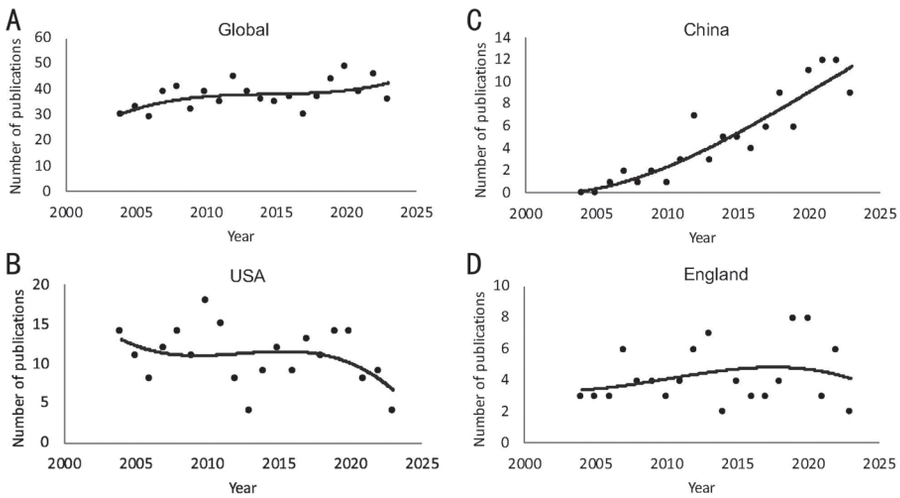

Figure 3 The fitting curves of publication growth trends in microphthalmos and anophthalmos research A: Global; B: USA; C: China; D: England.

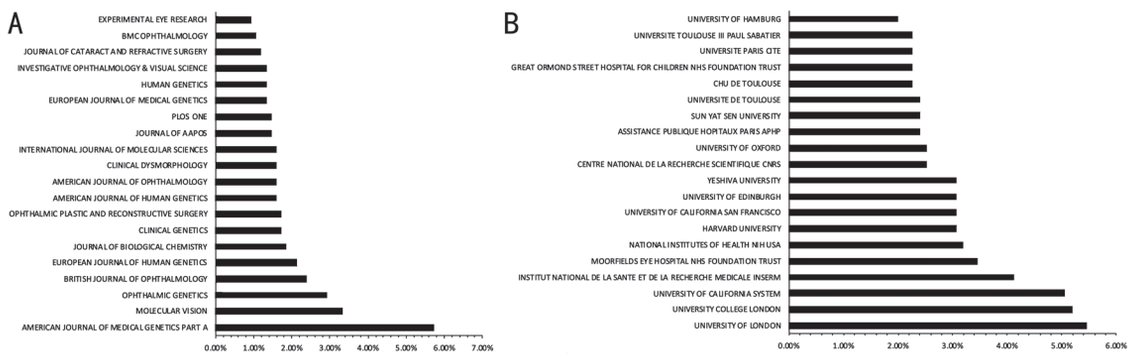

Figure 4 Distribution of journals and institutions relating to microphthalmos and anophthalmos A: The top 20 journals distributed the most research in this field; B: The top 20 institutions distributed the most research in this field.

has the highest number of published works, although there has been a decline in recent times. China, on the other hand, has displayed a considerable increase in publications over the past two decades. Although the publications of England fluctuated, the change was not significant and tended to be stable (Figure 3).

Distribution of Journal and Institutions Figure 4A illustrates that over 40.2% of the research papers were featured in the top 20 journals, which accounts for 302 papers. *American Journal of Medical Genetics Part A* published the most papers (43, 5.73%), followed by *Molecular Vision* (25, 3.33%). *Ophthalmic Genetics* and *British Journal of Opthalmology* ranked third and fourth with 22 (2.93%) and 18 (2.40%) publications, respectively. In the past twenty years, the *European Journal of Human Genetics* and the *American Journal of Human Genetics* have also published a significant number of articles, with 16 and 12 publications, respectively. The University of London has the largest number of M/A publications, with 41 articles accounting for 5.46% of the total publications, followed by the University College of London (39 articles, 5.19%) and the University of California system (38 articles, 5.06%). The top 20 institutions included 4 USA institutions, 15 European institutions, and 1 Chinese institution.

Author Distribution and Highly Cited Papers The top 15 authors published 145 papers, accounting for 19.31% of the total literature. The one who published the most on the subject of M/A was Schneider A from Yeshiva University, USA, with Chassaing N from CHU de Toulouse, France coming in second (Table 1). Table 2[3,31-39] displays the top 10 papers related to M/A that have been highly cited. The most frequently cited paper, with a total of 275 citations, was published by Pasutto *et al*[33], in the *American Journal of Human Genetics*.

Co-occurrence Analysis of Keywords for M/A According to VOSviewer, keywords were categorized into three main clusters: gene expression-related studies, clinical phenotype-related studies, and comorbidity and complication-related studies (Figure 5A). In the gene expression research cluster, gene (96 times), expression (98 times), and mitf (92 times) were frequently mentioned. In the cluster of clinical phenotype-related studies, the keywords “coloboma” and “defects” were mentioned 54 and 30 times, respectively. The keywords “posterior microphthalmos” (40 times) and angle-closure glaucoma (25 times) were frequently mentioned in the comorbidities and complications cluster.

The time of appearance of the keywords was represented by average appearance year and the colors used to highlight them

Table 1 Top 10 authors with the most publications in microphthalmos and anophthalmos

Top 10 authors	Country/regions	Affliation	Publications	Citations	H-index
Schneider A	USA	Yeshiva University	23	1231	17
Chassaing N	France	CHU de Toulouse	16	543	11
Calvas P	France	CHU de Toulouse	15	548	11
Zenteno JC	Mexico	Inst Ophthalmol Conde Valenciana	15	472	12
Bardakjian T	USA	Yeshiva University	14	557	11
Ragge N	England	University of Oxford	14	721	12
Fitzpatrick DR	Scotland	University of Edinburgh	12	1307	11
Kutsche K	Germany	University of Hamburg	12	386	9
Li DM	China	Capital Medical University	12	78	5
Reis LM	USA	Medical College of Wisconsin	12	452	10

Table 2 Top 10 high-cited papers related to microphthalmos and anophthalmos

TOP10 high cited papers	Corresponding authors	Journal	Publication year	Total citations
Mutations in STRA6 cause a broad spectrum of malformations including anophthalmia, congenital heart defects, diaphragmatic hernia, alveolar capillary dysplasia, lung hypoplasia, and mental retardation	Anita Rauch[33]	*AMERICAN JOURNAL OF HUMAN GENETICS*	2007	275
Fifteen-year quest for microphthalmia-associated transcription factor target genes	Corine Bertolotto [31]	*PIGMENT CELL & MELANOMA RESEARCH*	2010	266
Anophthalmia and microphthalmia	David R Fitzpatrick[3]	*ORPHANET JOURNAL OF RARE DISEASES*	2007	250
Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in BCOR	Graeme C M Black[34]	*NATURE GENETICS*	2004	239
SOX2 anophthalmia syndrome	David R Fitzpatrick[35]	*AMERICAN JOURNAL OF MEDICAL GENETICS PART A*	2005	176
The genetic architecture of microphthalmia, anophthalmia and coloboma	David R Fitzpatrick[32]	*EUROPEAN JOURNAL OF MEDICAL GENETICS*	2014	174
Mutations in SOX2 cause anophthalmia-esophageal-genital (AEG) syndrome	David R Fitzpatrick[36]	*HUMAN MOLECULAR GENETICS*	2006	166
Mutations in the human RAX homeobox gene in a patient with anophthalmia and sclerocornea	Peter H Mathers[37]	*HUMAN MOLECULAR GENETICS*	2004	161
Mutations of VMD2 splicing regulators cause nanophthalmos and autosomal dominant vitreoretinochoroidopathy (ADVIRC)	Graeme C M Black[38]	*INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE*	2004	160
The microphthalmia-associated transcription factor Mitf interacts with β-catenin to determine target gene expression	Eirikur Steingrimsson[39]	*MOLECULAR AND CELLULAR BIOLOGY*	2006	140

(Figure 5B). The keywords that appeared earlier, such as "gene (2012)", were highlighted in blue. Keywords shown in yellow were recent ones, for example, optical coherence tomography (2018).

According to the topic trend (Figure 6), we find that the hotspots change from year to year. "Microphthalmia transcription factor" is the earliest hotspot in the past 20y, which lasted until 2015. As time passes by, the hotspots have gradually changed, and "orbit" is the hotspot that has gained significance between 2021 and 2022.

DISCUSSION

This study demonstrates annual publications and trends in M/A-related research in various countries/regions. We found that M/A-related research has gained increasing attention in recent years. It's important to note that most of the top 20 institutions involved in M/A are located in Europe and the USA and the number of publications was highest in the USA. USA leads in this area due to its substantial and diverse funding sources, world-class research expertise, supportive healthcare infrastructure, and its influential role in global research collaborations. These factors collectively foster continuous innovation and advancement in this area. We observed a steady rise in the annual quantity of M/A-related publications across the globe on the timeline. By 2021, China surpassed the USA and held the most publications for the first time, demonstrating the important contribution of Chinese scholars to the field. China's surge in M/A advancement since 2004 could be linked to the progress of research facilities in China. It is worth mentioning that the citation frequency and H-index of China are much lower than those of the USA. There is only one Chinese institution in the top 20 institutions. Several reasons may explain this situation. Just as we mentioned before, the assessment and treatment of M/A have not been standardized in China. In addition, medical resources in Chinese hospitals are uneven and there is a lack of large-scale clinical studies. Although, the prediction curve shows a clear upward trend in the amount of literature in China, researchers and clinicians still need to strive for advancements in this area.

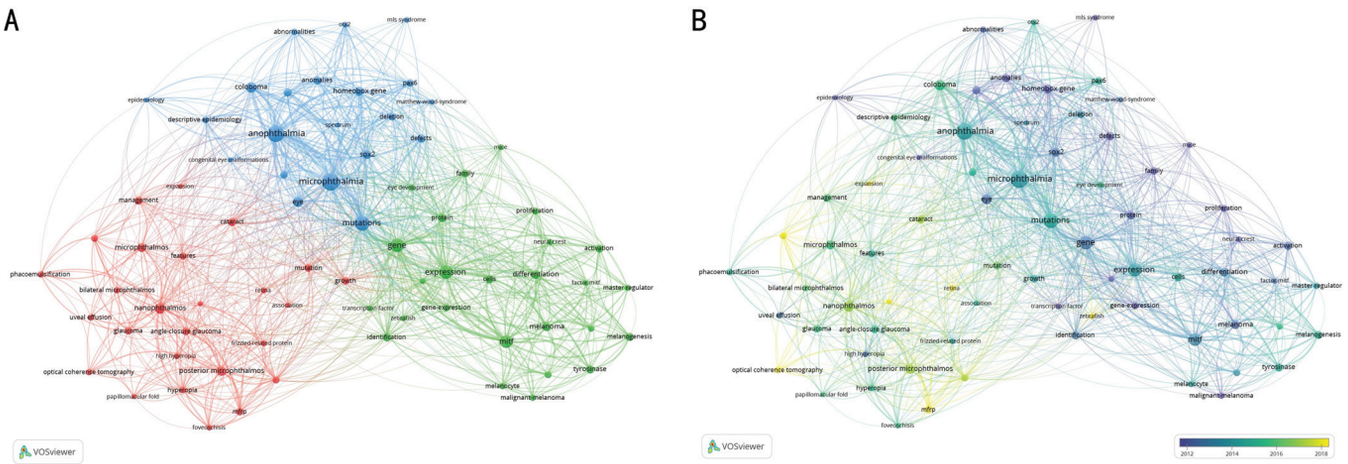

Figure 5 Analysis of keywords on microphthalmos and anophthalmos A: Mapping of the keywords on microphthalmos and anophthalmos; B: Distribution of keywords according to the average appearance time. mfrp: Membrane frizzled-related protein; mitf: Microphthalmia-associated transcription factor.

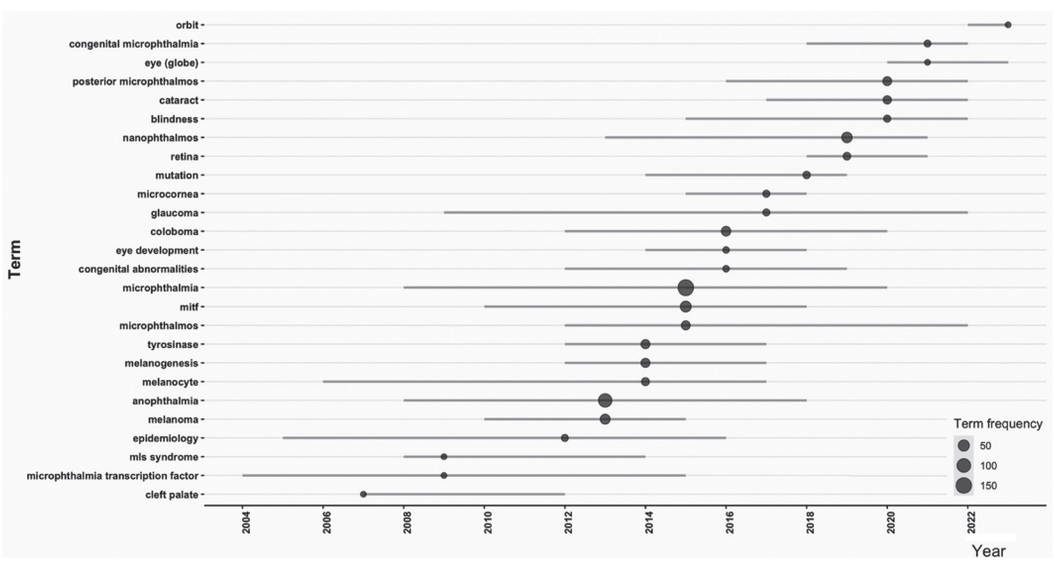

Figure 6 Top 24 topic trends in microphthalmos and anophthalmos mitf: Microphthalmia-associated transcription factor; mls syndrome: Microphthalmia with linear skin defects syndrome.

This study also showed that the *American Journal of Medical Genetics Part A*, *Molecular Vision*, *Ophthalmic Genetics*, and *British Journal of Opthalmology* were the leading journals in this field, ahead of other journals. In addition to journals related to ophthalmology research, there were also many studies published in high-scoring biology journals related to genes, dedicated to genetic mechanisms of M/A[40-42]. Leading research is mainly concentrated in basic science journals, and we found that highly cited articles are also concentrated in basic science. However, most of these articles mainly appeared in the first decade of the 21st century, and in the past decade, the focus has been on the intervention and treatment of M/A. This phenomenon shows that the genetic and molecular mechanisms of M/A are complex so that researchers' understanding of M/A is still insufficient. Due to the urgency of clinical treatment, researchers and clinical scientists have shifted their attention to intervention treatment.

The researchers Schneider A from the USA, Chassaing N from France, and Calvas P from France have contributed significantly to the field of M/A by publishing the highest number of articles. Their research focused on identifying mutations in genes associated with microphthalmia and anophthalmia, such as *SRY-Box 2* (*SOX2*), *FOXE3*, and *STRA6*[33,43-45]. These scientists have played an irreplaceable and unique role in shaping the field, influencing its development, and guiding clinical practices. By analyzing the works of these authors, we can identify the key research directions in the field. This article lists the top 10 most cited papers related to M/A. The impact of a publication in an academic field is directly proportional to the number of citations it receives. As of 2024, these 10 articles have been cited a total of 2007 times. In these studies, researchers primarily investigated the genetic mutations, inheritance patterns, and downstream pathogenic pathways underlying congenital microphthalmia and

anophthalmia. They identified several common pathogenic genes, such as *SOX2* and *OTX2*. Additionally, they reported some specific diseases characterized by microphthalmia and anophthalmia phenotypes, which often have their own specific pathogenic genes. These findings are of great significance for clinical diagnosis, as genetic testing can serve as the gold standard for diagnosis and provide disease classification. For diseases with potential genetic risks, prenatal diagnosis can be performed based on these findings. However, we must admit that even though we have clarified part of the pathogenesis, there are no effective treatments targeting genetic mutations. If we could initiate gene therapy for these patients at an early stage, it might have a significant therapeutic effect on the development of the eyeball and orbit. Of course, this would require substantial efforts from researchers in future attempts.

Keyword network analysis shows that the recent trend of research has gradually shifted from genetic mechanisms to different clinical phenotypes and corresponding clinical interventions. We also found that in the last decade, microphthalmia-related ocular comorbidities received increasing attention from researchers, such as the keywords "cataract", "glaucoma", and "retina"[46-48]. "Posterior microphthalmos" is a new high-mentioned keyword that has appeared since 2016, which disproportionately affects the posterior segment of the eye and has no anomalies in front of the eye[49-51]. This indicated that our research tended to focus on special clinical cases, and different phenotypes brought by gene mutations may be the hotspot of research in the future. We also found that "orbit" was a new word that popped up in 2022, which indicated that the idea of orbital development required the stimulatory effect of the eyeball began to receive attention[52]. This includes addressing issues such as orbitofacial development and the psychological well-being of affected children. Additionally, the intricate genetic and molecular mechanisms underlying M/A remain poorly understood[53]. Despite a brief surge in research activity in the early 20th century, there is a need for ongoing and intensified research efforts in this area. Researchers must persist in their investigations to unravel these complex mechanisms and improve overall disease management strategies[54].

We conducted a comprehensive and objective data analysis of publications related to M/A, extracted from the Web of Science database. However, there are certain limitations to our study. Although the Web of Science is typically seen as thorough in its scope, it does not completely include all scholarly literature. Consequently, certain vital publications not included in this database may inadvertently be disregarded. Besides, the predominance of English-language journals in the Web of Science may also result in the underrepresentation of important research published in other languages. To ensure more scientific search strategies and the inclusion of publications in multiple languages, future research should be conducted. What's more, our analysis was limited to publications from the past 20y, and further studies may consider a broader time frame.

In conclusion, this study analyzes the M/A knowledge base over the past 20y. The clinical intervention for M/A has gained a lot of attention as an emerging area of interest. This implies that in addition to focusing on the disease itself, we should also focus on the overall management of the disease, such as orbitofacial development and children's psychological problems. Moreover, due to the complexity of the genetic and molecular mechanisms of M/A, it is still unclear. Although there was a small peak in research in this direction in the early 20th century, researchers should continue to work hard.

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