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Progress and prospects of gene therapy in ophthalmology from 2000 to 2022: A bibliometric analysis

Bingyan Li [a,b,c,1], Wei Tan [a,b,c,1], Zicong Wang [a,b,c], Haixiang Zhou [a,b,c], Jingling Zou [a,b,c], Yun Li [a,b,c], Shigeo Yoshida [d], Yedi Zhou [a,b,c,*]

[a] Department of Ophthalmology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China
[b] Hunan Clinical Research Center of Ophthalmic Disease, Changsha, Hunan, 410011, China
[c] National Clinical Research Center for Metabolic Diseases, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China
[d] Department of Ophthalmology, Kurume University School of Medicine, Kurume, Fukuoka, 830-0011, Japan

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ABSTRACT

Background: Gene therapy is a treatment approach at the genetic level, which brings great advances in many diseases and develops rapidly in recent years. Currently, its mechanism of action is mainly through the replacement of missing or defective genes, or the reduction of harmful gene products. However, the application of gene therapy in ophthalmology remains limited.
Methods: A total of 1143 articles and reviews published in the field of ocular gene therapies were found in the Web of Science Core Collection database and used for the bibliometric analysis. CiteSpace was mainly applied to the network analysis of countries, institutions, keywords, and dual-map overlay of journals. The visual analysis of authors, journals, and references was used by VOSviewer. The geographical distribution of publications was conducted by R language.
Results: The annual publications are increasing in general. Currently, the USA and the UK are two main sources of publications in this field. Switzerland, Denmark, and Finland are the top 3 countries that establish the most cooperation and exchanges with other countries or regions. The most cited and co-cited journal in this field is *Investigative Ophthalmology & Visual Science*. Gene therapy studies for eye diseases are mainly focused on retinal dysfunctions by the analysis of references, keywords, and counting of original research, including Leber's congenital amaurosis and retinitis pigmentosa.
Conclusion: This study used bibliometrics to analyze overall characteristics and put forward prospects for the future in the field of gene therapy in ophthalmology. Ocular diseases, especially hereditary retinal diseases, will be the major focus of gene therapy in the future.

1. Introduction

Increasing independent research has indicated that gene therapy aims to achieve long-term improvement or cure diseases by transferring genetic material to patients [1–3]. Gene replacement, gene silencing, gene addition, and gene editing are the four main

* Corresponding author. Department of Ophthalmology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China.
E-mail address: zhouyedi@csu.edu.cn (Y. Zhou).
[1] Bingyan Li and Wei Tan contributed equally to this work.

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strategies of gene therapy [3]. Gene therapy techniques have been widely applied by using adeno-associated virus (AAV) vectors for gene delivery, CRISPR/Cas9 gene editing, and other approaches [4–7].

To date, clinical research related to gene therapy has been widely applied to various diseases, including cancer, ocular diseases, neurodegenerative diseases, cardiovascular diseases, etc [2,6–8]. In ophthalmology, genetic factors play a large part in the pathogenic role of retinal degeneration in monogenic and complex diseases [9,10]. The eye is a great target for gene vector delivery because it is an immune-privileged site, is directly visible, and has multiple ways to assess sensitivity [11,12]. In December 2017, the Food and Drug Administration approved the commercial use of voretigene neparvovec, which improves functional vision in previously untreatable *RPE65*-mediated hereditary retinal dystrophy [13–15]. Delivery techniques for ocular gene therapies include subretinal injections with pars plana vitrectomy, intravitreal injections, and suprachoroidal injections [16]. In addition, sustained effects may exist after a single injection making gene therapy to be an integral part of the ophthalmological clinical treatment [16,17].

Despite the enormous therapeutic potential of gene therapy, its safety and efficacy are being continuously validated and improved in animal experiments and clinical studies [18]. The translation from animal experiments to clinical studies faces numerous challenges, such as gene delivery methods, incomplete understanding of disease molecular mechanisms, low concentrations of gene products at target sites, and differences between animal models and human diseases [19]. Moreover, it is needed to summarize the features and research topics for gene therapy in ocular diseases. Bibliometric analysis is a research tool to cluster literature and build a knowledge graph, providing the characteristics and development trends. Therefore, in this study, we conduct a bibliometric analysis of the current trends of gene therapy in ophthalmology.

The present study identified and analyzed publications on gene therapy of ophthalmology over the past 23 years, including the number of publications per year, authors, countries, journals, institutions, references, and keywords. The study aimed to clearly observe the ophthalmological development process, spatial density, areas of research interest, and directions for future research.

2. Methods

2.1. Data source and search strategy

The Web of Science Core Collection (WoSCC) is the largest citation database of science in the world, includes literature abstracts and citation information [20], and is the source of our data search and download. The search strategy is detailed in Fig. 1 and includes the following keywords and Boolean operators: Topic search #1 = ("Genetic Therapy" OR "Genetic Therapies" OR "DNA Therapy" OR "DNA Therapies" OR "Gene Therapy" OR "Gene Therapies" OR "RNAi-Based Therapeutics" OR "RNAi-Based Therapy" OR "RNAi Based Therapy" OR "RNAi-Based Therapies" OR "RNAi Therapy" OR "RNAi Therapies"); topic search #2 = ("Ophthalmology" OR "Eye" OR "Ocular Diseases" OR "Ocular Disease" OR "Eye Disease" OR "Eye Diseases" OR "Ophthalmic Disease" OR "Ophthalmic Diseases"); topic search #1 AND # 2.

After restrictions on language as English, and article types limited to article and review, 1191 documents published from Jan 1, 2000 to Dec 31, 2022 were exported from WoSCC. Data were exported in one day to avoid document changes in the condition of

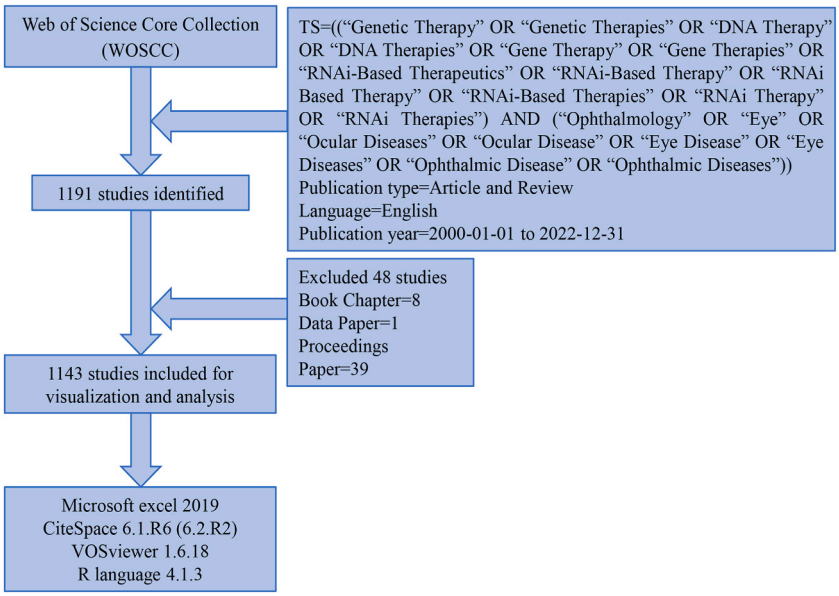


Fig. 1. Flowchart showing the bibliometric analysis: literature inclusion, exclusion and analysis process. A total of 1191 documents published between 2000 and 2022 were found after limiting language to English, restricting article types as articles and reviews. Of these, 48 book chapters, data papers or proceedings papers were excluded, and 1143 publications were used for subsequent bibliometric analysis.

updating of WoSCC database. Next, we filtered 48 redundant studies by CiteSpace (including 8 book chapters, 1 data paper, and 39 proceedings papers), remained 1143 studies for data analysis.

2.2. Data analysis

Using WoSCC, information on authors, institutions, countries, keywords, publication year, journals, and references were collected for subsequent analysis and discussion [21]. CiteSpace and VOSviewer are the main databases used for literature analysis in bibliometric studies, especially in the visualization of network maps and cluster analysis [22,23]. Each node symbolizes a country, institution, author, journal, or reference. A purple ring at a node indicates betweenness centrality, which means the occurrence of an important node in this field and implies significant influence; centrality functions as a hinge point, once a node links more of the other nodes in the figure, the country or institution which the node stands for have higher centrality. A line between nodes signifies a cooperative relationship between the countries or institutions, and the thickness of the line is closely associated with the closeness of cooperation [24,25]. Annual publications of gene therapy in ophthalmology and total publications of institutions are clarified using a histogram, pie charts, and the world map drawn by R language are used to show the publications of different countries.

3. Results

3.1. Publications in the field of gene therapy in ophthalmology by year

The number of publications in different periods provides an indication of the research interest in gene therapy of ophthalmology, reflecting the development and speed of this field. The specific number of publications per year from 2000 to 2022 is shown in Fig. 2 and is categorized as early (2000), growth (2001–2018), decline (2019), and flourishing stages (2020–2022). In the period 2000–2018, a steady upward trend of the total relevant publications is observed which implied that gene therapy was of increasing interest in academic circles. After one year of decline in 2019, numbers reached a peak in the years 2020–2022, suggesting gene therapy renewed from a trough and ushered in a new research climax.

3.2. Geographical distribution of published countries

According to the statistics, a total of 56 countries published relevant articles or reviews in this field (Supplemental Table 1). Color coding in Fig. 3A illustrates publications of different countries by the color depth of blue on the world map. The top 10 countries (with the highest publication numbers) distribute in North America (the United States (the USA) and Canada, n = 622), Europe (the United Kingdom (the UK), Germany, Italy, France, and Spain, n = 428), Asia (China and Japan, n = 168), and Oceania (Australia, n = 56). The detailed publications and percentages of top 10 countries are shown in Fig. 3B, indicating that more than half of publications are from the USA, the UK, and China (54%). Next, we constructed and visualized the cooperative network map and the relationship among countries using CiteSpace software (Fig. 3C). The green color ring represents the relevant articles published in a certain year which is proportional to publication numbers. The purple ring outside of the green ring acts on behalf of centrality. The thickness of the lines represent the degree of cooperation among countries. Countries with the highest number of publications such as the USA, the UK, and China are labeled with purple rings and more layers of green color, indicating that these countries maintain high research interest in this field throughout the period and play a vital role in the development of gene therapy in ophthalmology. Although Switzerland, Denmark, and Finland are not on the list of top 10 publications, they occupy the top 3 in centrality ranking with purple rings in Fig. 3C (details of all countries are listed in Supplemental Table 1), providing evidence that quantity is not the only criterion by which to judge the impact of papers. Moreover, cooperation and communication exist between multiple countries; for example, Switzerland establishes partnerships with the UK, Denmark, Finland, and Australia; China collaborates dynamically with the USA and Canada.

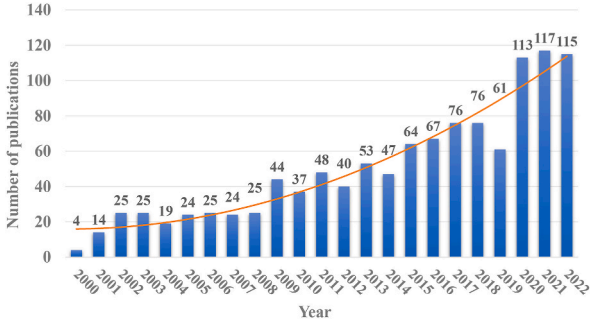
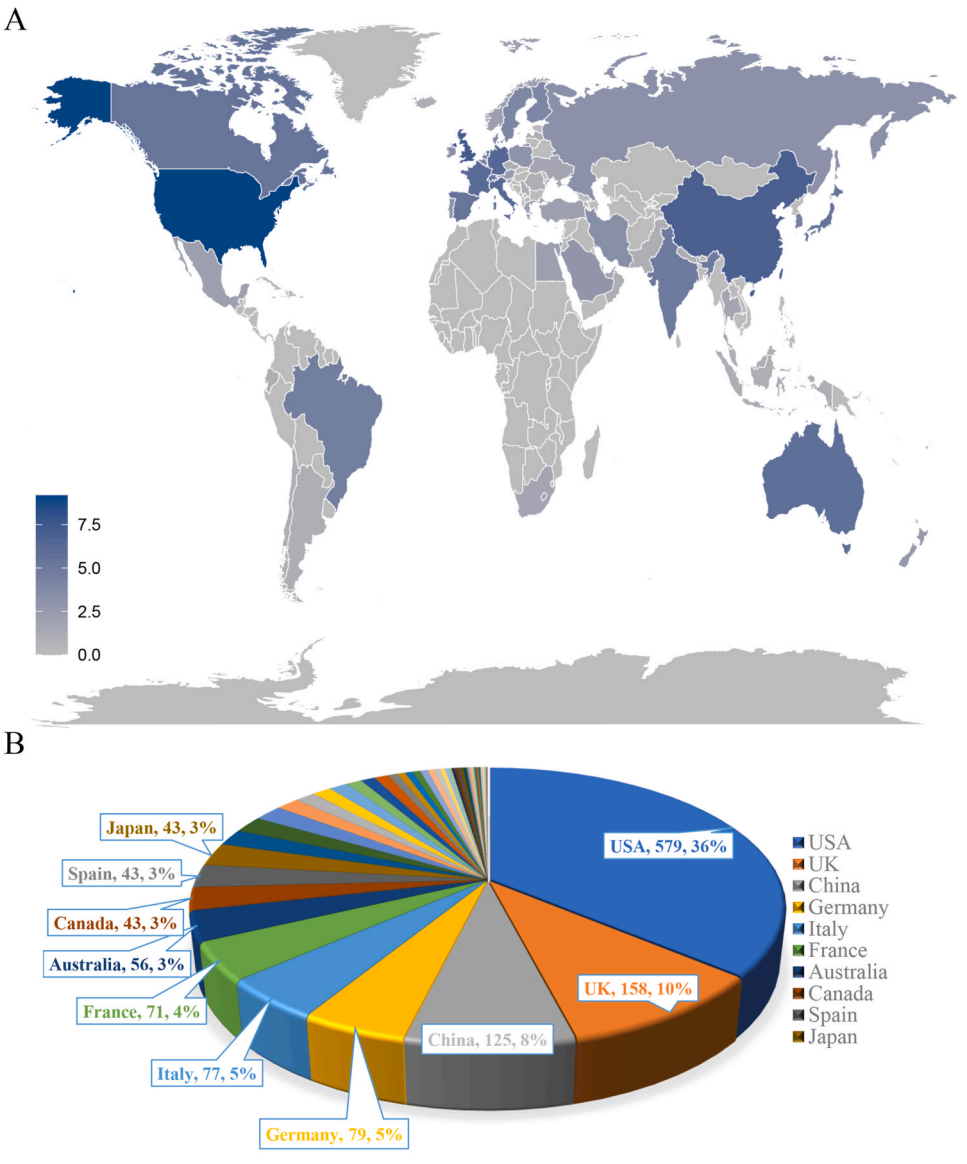


Fig. 2. Numbers of publications on gene therapy in ophthalmology by year.



(caption on next page)

Fig. 3. Visualization of geographical distribution and cooperation network among countries of authors in research on gene therapy in ophthalmology. (A) The world map labeled with the country. The color depth represents publication numbers of each country. (B) Publication numbers by country. Top 10 countries are labeled. (C) Co-authorship among countries that published at least 15 papers. Nodes, the green rings and purple rings mean countries, publications and centralities respectively. And the thickness of lines signifies the tightness of cooperation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3. Co-authorship of institutions

In total, 419 institutions published related papers and were involved in the studies of ophthalmology on gene therapy. The top 10 institutions producing these publications are shown in Fig. 4A. Papers from the University of Pennsylvania, the University of Florida, and University College London (UCL) are far ahead of all other institutions. The top 10 productive institutions are all affiliated with the USA (n = 7) and the UK (n = 3), consistent with the publication numbers. Moreover, the total number of institutions from the USA accounts for 127/419 (30.3%) in all institutions, and that from the UK occupies 32/419 (7.6%). The ranking of centralities is listed in Table 1, showing that the USA (n = 7) also is the home of most institutions, followed by the UK (n = 2) and France (n = 1). Subsequently, co-authorship visual analysis of institutions is constructed by setting the minimum number of publications of the agency to 15. As shown in Fig. 4B, active cooperation has been established among different institutions around the world. Children's Hospital of Philadelphia has the highest centrality establishing strong communication with 11 other institutions, such as Harvard Medical School, UCL, Ghent University, and University of Missouri. In contrast, many other institutions had no contact with others.

3.4. Author analysis of co-authorship and co-citation

The 1143 documents included 5593 authors, 129 of whom had published at least 5 papers. Co-authorship analysis was conducted by VOSviewer, the results of which are shown in Fig. 5A. A total of 129 authors are organized into 10 clusters with different colors, each representing a research team. The top 10 authors with no less than 10 publications are listed in Table 2, and the most productive

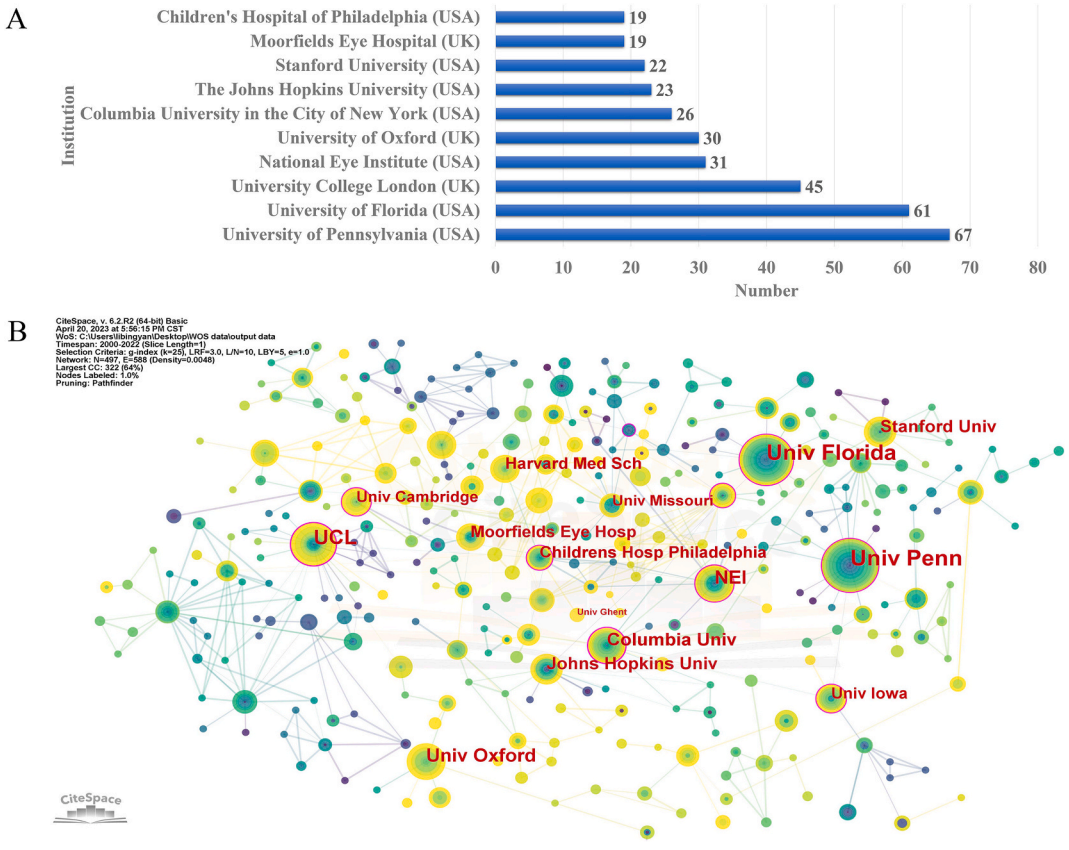


Fig. 4. Co-authorship among institutions on research in ophthalmological gene therapy. (A) The top 10 institutions in term of publications. (B) Distribution map and collaboration network among institutions. Nodes, the green rings and purple rings mean institutions, publications and centralities respectively. And the thickness of lines signifies the tightness of cooperation. NEI, National Eye Institute; UCL, University College London. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Top 10 institutions in ranking of centrality about gene therapy in ophthalmology.

Rank	Centrality	Institution (Country)
1	0.21	Children's Hospital of Philadelphia (USA)
2	0.2	Columbia University in the City of New York (USA)
3	0.19	University College London (UK)
4	0.15	University of Pennsylvania (USA)
5	0.15	Centre national de la recherche scientifique (France)
6	0.12	University of Florida (USA)
7	0.12	University of Oxford (UK)
8	0.12	The University of Iowa (USA)
9	0.12	The Jackson Laboratory (USA)
10	0.11	Harvard Medical School (USA)

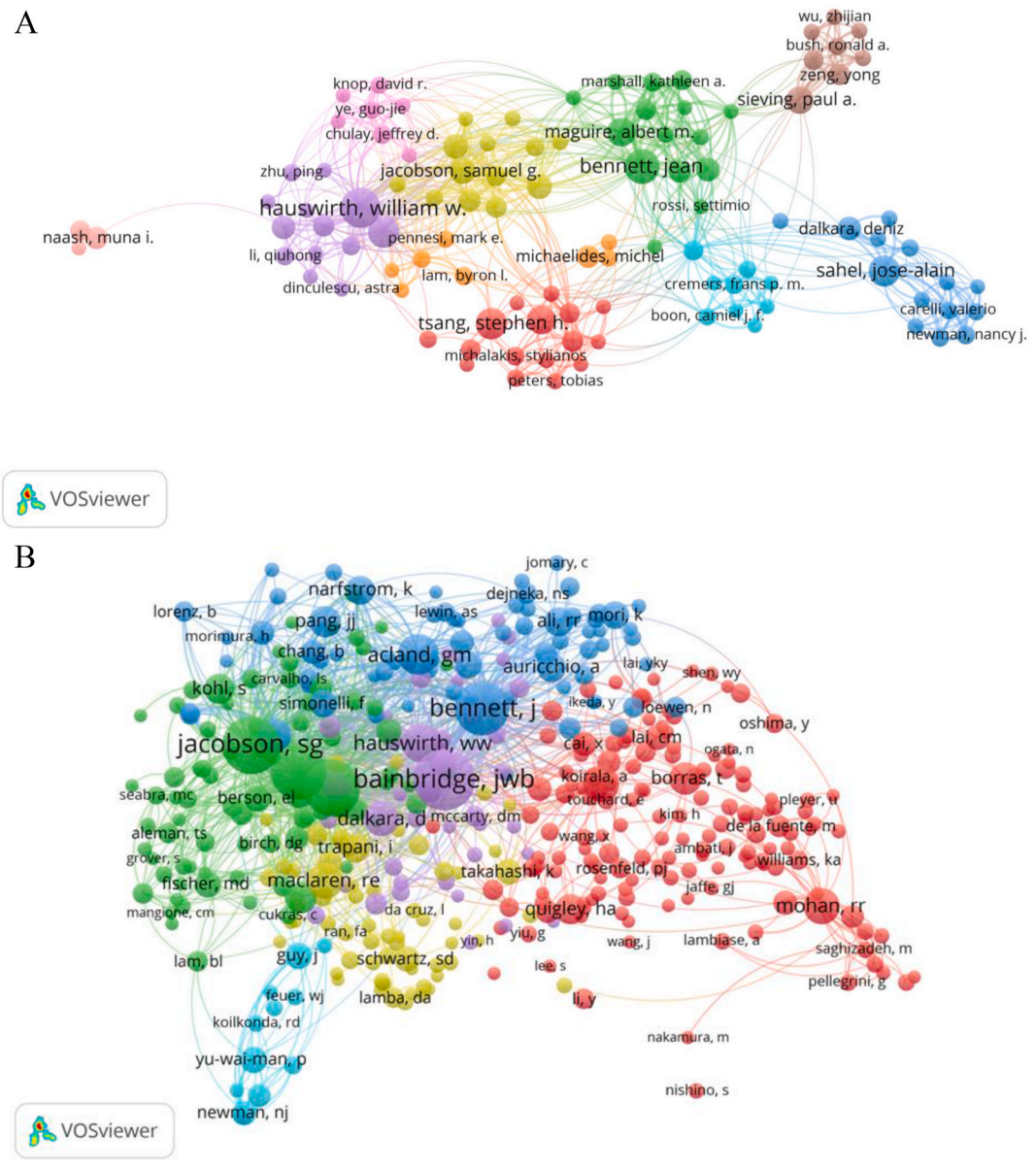


Fig. 5. Visualization analysis of co-authorship and co-citation. (A) Co-authorship of 129 authors who had published at least 5 papers. Each color indicates one of ten clusters. (B) Co-citation analysis of 431 authors with more than 20 publications, showing 6 clusters. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Top 10 authors in terms of publications and co-citation.

Rank	Author	Publications	Centrality	Co-cited Author	Co-citations
1	William W Hauswirth	29	0.03	James W B Bainbridge	429
2	Jean Bennett	23	0.03	Samuel G Jacobson	382
3	José-Alain Sahel	15	0.01	Albert M Maguire	368
4	Sanford L Boye	14	0.03	Artur V Cideciyan	355
5	Stephen H Tsang	13	0.01	Jean Bennett	335
6	Tomas S Aleman	12	0.04	Gregory M Acland	194
7	Paul A Sieving	11	0	William W Hauswirth	166
8	Robert E MacLaren	11	0.02	Rajiv R Mohan	152
9	M Dominik Fischer	10	0.01	Peter A Campochiaro	149
10	Artur V Cideciyan	10	0.01	Robert E MacLaren	149

author is William W Hauswirth. The centrality for one author means his contribution to this research field or significant reference of their papers to other scholars, which can be manifested as the number of citations and co-citations. We found that the rankings of centrality and publication are not consistent for the same author, which reflects that publications are not directly proportional to the quality and influence of one paper. Co-citation means authors, journals, or references of two or more papers are cited by the other paper at the same time. The top 10 authors of co-citation are shown in Table 2, where James W B Bainbridge occupies the first place with a co-citation number of 429. For co-citation author visualization, we selected 431 authors who had been co-cited at least 20 times. As Fig. 5B illustrates, 6 clusters were determined, the largest of which includes 152 authors followed by clusters with 85, 74, 64, 43, and 13 authors.

3.4. Top 10 cited journals and co-cited journals

Publications were distributed among 247 journals, and Table 3 shows the top 10 cited journals and co-cited journals. The top-ranked journal based on citation counts is *Investigative Ophthalmology & Visual Science* with 944 citations (Journal Citation Reports Quarter 1 (JCR Q1), the impact factor (IF) = 4.925), the second is *Proceedings of the National Academy of Sciences of the United States of America* with 776 citations (JCR Q1, IF = 12.779), and the third is *Molecular Therapy* with 655 citations (JCR Q1, IF = 12.910). Less than half of the journals are specific to the field of ophthalmology.

The analysis of co-cited journals was based on 581 journals that had been cited at least 15 times. As shown in Fig. 6A, the network of co-citation was created using VOSviewer and divided into 6 clusters here. The top 3 rankings are *Investigative Ophthalmology & Visual Science* with 6257 co-citations, *Molecular Therapy* with 2483 co-citations, and *Proceedings of the National Academy of Sciences of the United States of America* with 2461 co-citations, respectively. It is almost the same as the cited journal. Fig. 6B shows a visualization of citation links in the field of gene therapy in ophthalmology. The left scatter point stands for citing journal, the right scatter point stands for cited journal, and the color distinguishes the discipline of the journal source. The thickness of the citation link represents the closeness of the research content of the journal in which the research is published or cited. The figure indicates clearly that the citing journals from molecular aspects, biology, and immunology (citation link of yellow), neurology, sports, and ophthalmology (citation link of pink) have the closest relationship of cited journals which source from molecular aspects, biology, and genetics.

Table 3
Top 10 cited or co-cited journals.

Rank	Journal	Counts	JCR (2021)	IF (2021)	Co-cited journal	Counts	JCR (2021)	IF (2021)
1	Investigative Ophthalmology & Visual Science	944	Q1	4.925	Investigative Ophthalmology & Visual Science	6257	Q1	4.925
2	Proceedings of the National Academy of Sciences of the United States of America	776	Q1	12.779	Molecular Therapy	2483	Q1	12.910
3	Molecular Therapy	655	Q1	12.910	Proceedings of the National Academy of Sciences of the United States of America	2461	Q1	12.779
4	Human Gene Therapy	594	Q1	4.793	Gene Therapy	1953	Q2	4.184
5	Gene Therapy	576	Q2	4.184	Ophthalmology	1683	Q1	14.277
6	Experimental Eye Research	574	Q2	4.770	Human Gene Therapy	1669	Q1	4.793
7	Ophthalmology	547	Q1	14.277	Experimental Eye Research	1455	Q2	4.770
8	PLoS One	522	Q2	3.752	PLoS One	1245	Q2	3.752
9	the New England Journal of Medicine	519	Q1	176.079	Archives of Ophthalmology	1174	–	–
10	Archives of Ophthalmology	512	–	–	the New England Journal of Medicine	1153	Q1	176.079

JCR Q1, Journal Citation Reports Quarter 1; IF, impact factor.

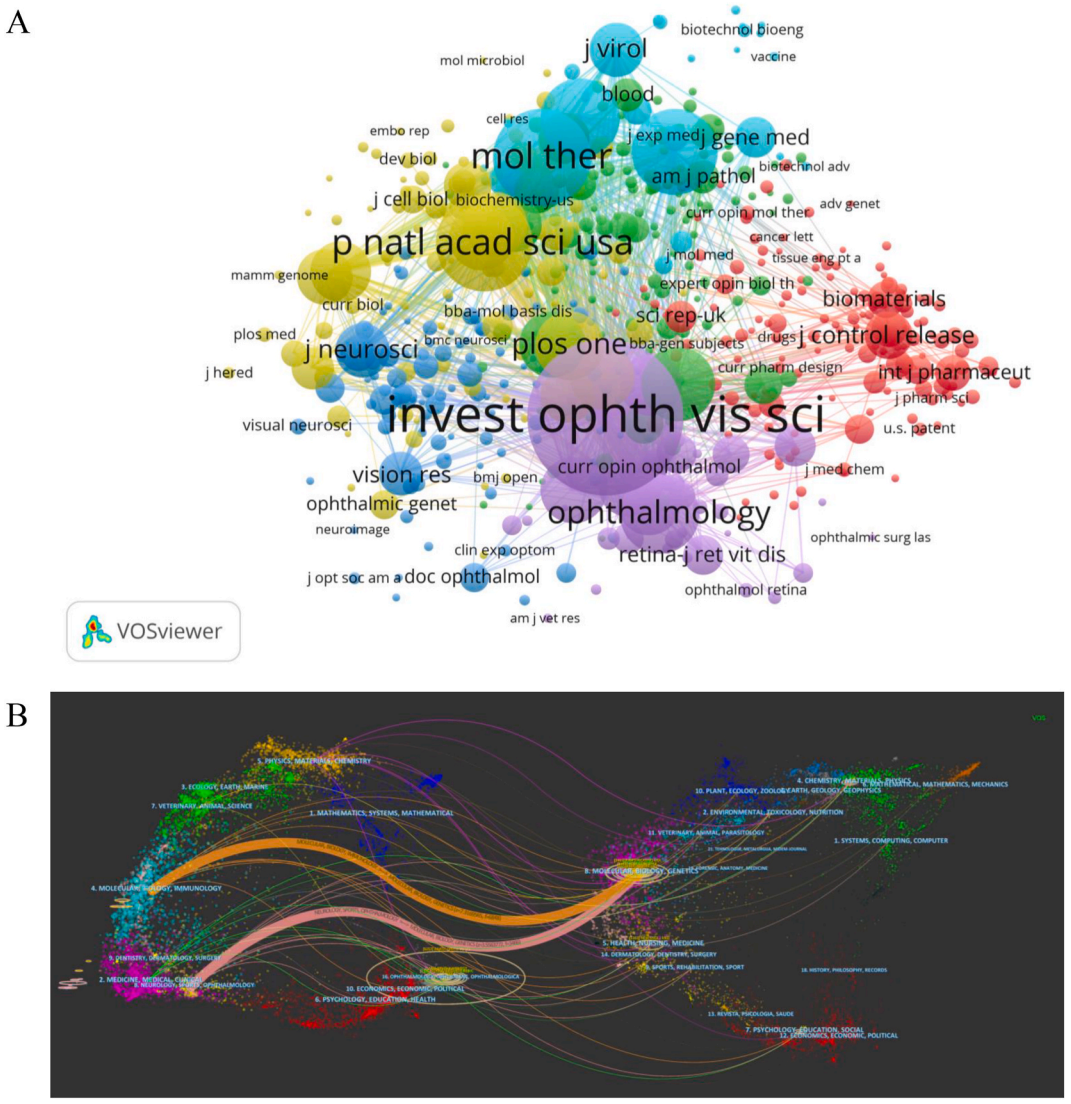


Fig. 6. Network diagram in gene therapy journals. (A) Co-citation map of journal with the threshold of 15 times. Journals are divided into 6 clusters by colors. (B) Dual-map overlay of journals in which research was published (left) or cited (right). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.5. High-cited and co-citation references

Citation frequency can reflect the influence and interest of an article in the field of research. The total number of co-cited references included in the analysis by VOSviewer was 179. Fig. 7A shows clearly that reference with the strongest citation bursts was published in 2008 and was named effect of gene therapy on visual function in Leber's congenital amaurosis (LCA), the second was also published in 2008 and was on the efficacy and safety of gene transfer therapy for LCA, and both of them were published in the journal of *the New England Journal of Medicine*. Four clusters of co-citation analysis by VOSviewer are shown in Fig. 7B, where larger nodes indicate higher co-citation frequencies. VOSviewer automatically identifies the correlation between various literature and distinguishes clusters by colors of red, green, blue, and yellow, which stands for 75, 66, 28, and 10 references.

As shown in Table 4, the most frequently cited paper is named efficacy and safety of voretigene neparvovec (AAV2-h*RPE65*v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomized, controlled, open-label, phase 3 trial. It was published in 2017 in *Lancet* and had been cited 103 times to the date of analysis. Of the top 10 cited references, 3 publications are from the *Lancet* and 4 papers are from *the New England Journal of Medicine*. Two papers are authored by James W B Bainbridge, and Samuel G Jacobson published two papers as well. As shown by Table 5, the most frequently co-cited paper is titled gene therapy restores vision in a canine model of childhood blindness. Its co-citation frequency is 129.

A

Top 20 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2000 - 2022
Acland GM, 2001, NAT GENET, V28, P92, DOI 10.1038/ng0501-92, DOI	2001	19.65	2001	2006	
Acland GM, 2005, MOL THER, V12, P1072, DOI 10.1016/j.ymthe.2005.08.008, DOI	2005	12.94	2006	2010	
Maguire AM, 2008, NEW ENGL J MED, V358, P2240, DOI 10.1056/NEJMoa0802315, DOI	2008	36.37	2008	2013	
Bainbridge JWB, 2008, NEW ENGL J MED, V358, P2231, DOI 10.1056/NEJMoa0802268, DOI	2008	42.95	2009	2013	
Hauswirth WW, 2008, HUM GENE THER, V19, P979, DOI 10.1089/hum.2008.107, DOI	2008	20.83	2009	2013	
Cideciyan AV, 2008, P NATL ACAD SCI USA, V105, P15112, DOI 10.1073/pnas.0807027105, DOI	2008	17.09	2009	2013	
Allocca M, 2008, J CLIN INVEST, V118, P1955, DOI 10.1172/JCI34316, DOI	2008	9.19	2009	2013	
Maguire AM, 2009, LANCET, V374, P1597, DOI 10.1016/S0140-6736(09)61836-5, DOI	2009	17.41	2010	2014	
Simonelli F, 2010, MOL THER, V18, P643, DOI 10.1038/mt.2009.277, DOI	2010	16.56	2010	2015	
Bennett J, 2012, SCI TRANSL MED, V4, P0, DOI 10.1126/scitranslmed.3002865, DOI	2012	11.73	2012	2017	
Jacobson SG, 2012, ARCH OPHTHALMOL-CHIC, V130, P9, DOI 10.1001/archophthalmol.2011.298, DOI	2012	20.05	2013	2017	
Cideciyan AV, 2013, P NATL ACAD SCI USA, V110, PE517, DOI 10.1073/pnas.1218933110, DOI	2013	15.55	2014	2018	
Testa F, 2013, OPHTHALMOLOGY, V120, P1283, DOI 10.1016/j.ophtha.2012.11.048, DOI	2013	12.07	2014	2018	
Dalkara D, 2013, SCI TRANSL MED, V5, P0, DOI 10.1126/scitranslmed.3005708, DOI	2013	12.07	2014	2018	
MacLaren RE, 2014, LANCET, V383, P1129, DOI 10.1016/S0140-6736(13)62117-0, DOI	2014	28.62	2015	2019	
Jacobson SG, 2015, NEW ENGL J MED, V372, P1920, DOI 10.1056/NEJMoa1412965, DOI	2015	15.53	2015	2020	
Bainbridge JWB, 2015, NEW ENGL J MED, V372, P1887, DOI 10.1056/NEJMoa1414221, DOI	2015	23.74	2016	2020	
Schwartz SD, 2015, LANCET, V385, P509, DOI 10.1016/S0140-6736(14)61376-3, DOI	2015	8.44	2016	2020	
Feuer WJ, 2016, OPHTHALMOLOGY, V123, P558, DOI 10.1016/j.ophtha.2015.10.025, DOI	2016	8.28	2016	2022	
Bennett J, 2016, LANCET, V388, P661, DOI 10.1016/S0140-6736(16)30371-3, DOI	2016	16.8	2017	2022	

B

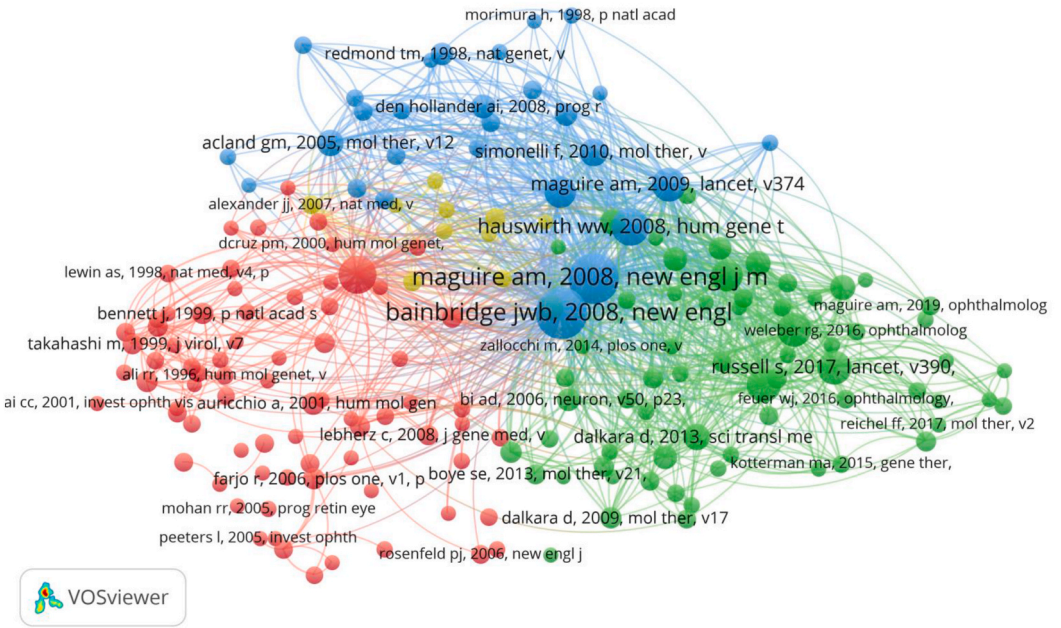


Fig. 7. Network diagram on gene therapy citation. (A) Top 20 references with the strongest citation bursts by year. (B) A distribution map of co-citation of references. Each node or color represents one reference or cluster. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.6. Keyword analysis

Keywords can provide indications of the present research focus and future research directions. We used CiteSpace to analyze keywords. In Fig. 8A, the nodes represent keywords, the size of the nodes represents the frequency of keywords, and the lines represent the relationship among them. The top 20 keywords with the strongest citation bursts are shown from 2000 to 2022 in Fig. 8B, the red line represents the time frame for keyword outbreak. The top-ranked keyword "gene transfer" appeared in 2001 and remained a research focus for 10 years, suggesting that the process of gene delivery may be a stable research component in ophthalmology in the decade. From 2017 to 2022, the keywords with the strongest citation bursts were macular degeneration (2017–2019), subretinal injection (2017–2019), gene editing (2018–2022), cell therapy (2019–2022), and retinal dystrophy (2020–2022). As detailed in Table 6, the top 20 keywords in ophthalmology are gene therapy, animal model, viral vector, in vivo, congenital amaurosis, retinitis pigmentosa, delivery, expression mutation, macular degeneration, retinal pigment epithelium, stem cell, retinal ganglion cell, therapy, retinal degeneration, photoreceptor, visual acuity, nanoparticle, transduction, choroidal neovascularization. The top-ranked keyword "gene therapy" was cited 618 times, and 12 other keywords were cited over 100 times. Six keywords were related to the retina, namely

Table 4
Top 10 cited papers on gene therapy in ophthalmology.

Rank	Title	First Author	Cited Frequency	Journal	Year
1	Efficacy and safety of voretigene neparvovec (AAV2-h*RPE65*v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial	Stephen Russell	103	Lancet	2017
2	Effect of gene therapy on visual function in Leber's congenital amaurosis	James W B Bainbridge	96	The New England Journal of Medicine	2008
3	Safety and efficacy of gene transfer for Leber's congenital amaurosis	Albert M Maguire	82	The New England Journal of Medicine	2008
4	Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial	Robert E MacLaren	70	Lancet	2014
5	Long-term effect of gene therapy on Leber's congenital amaurosis	James W B Bainbridge	67	The New England Journal of Medicine	2015
6	Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by *RPE65* mutations: a follow-on phase 1 trial	Jean Bennett	48	Lancet	2016
7	Gene therapy for leber congenital amaurosis caused by *RPE65* mutations: safety and efficacy in 15 children and adults followed up to 3 years	Samuel G Jacobson	46	Archives of Ophthalmology	2012
8	Improvement and decline in vision with gene therapy in childhood blindness	Samuel G Jacobson	45	The New England Journal of Medicine	2015
9	Treatment of leber congenital amaurosis due to *RPE65* mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial	William W Hauswirth	45	Human Gene Therapy	2008
10	Gene therapy for Leber's congenital amaurosis is safe and effective through 1.5 years after vector administration	Francesca Simonelli	39	Molecular Therapy	2010

Table 5
Top 10 co-citated papers on gene therapy in ophthalmology.

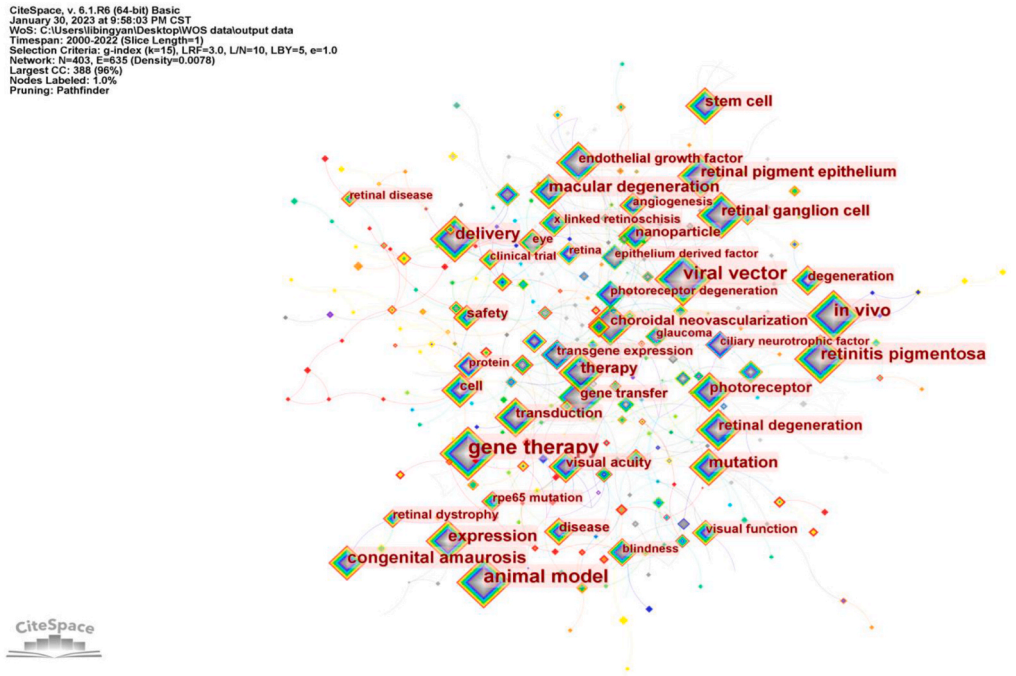
Rank	Title	First Author	Counts	Journal	Year
1	Gene therapy restores vision in a canine model of childhood blindness	Gregory M Acland	129	Nature Genetics	2001
2	Long-term restoration of rod and cone vision by single dose rAAV-mediated gene transfer to the retina in a canine model of childhood blindness	Gregory M Acland	63	Molecular Therapy	2005
3	Congenital stationary night blindness in the dog: common mutation in the *RPE65* gene indicates founder effect	G D Aguirre	20	Molecular Vision	1988
4	Restoration of cone vision in a mouse model of achromatopsia	John J Alexander	33	Nature Medicine	2007
5	Gene transfer into the mouse retina mediated by an adeno-associated viral vector	R R Ali	29	Human Molecular genetics	1996
6	Adeno-associated virus gene transfer to mouse retina	R R Ali	20	Human Gene Therapy	1998
7	Restoration of photoreceptor ultrastructure and function in retinal degeneration slow mice by gene therapy	R R Ali	34	Nature Genetics	2000
8	Novel adeno-associated virus serotypes efficiently transduce murine photoreceptors	Mariacarmela Allocca	25	Journal of Virology	2007
9	Serotype-dependent packaging of large genes in adeno-associated viral vectors results in effective gene delivery in mice	Mariacarmela Allocca	30	The Journal of Clinical Investigation	2008
10	Safety and efficacy of subretinal readministration of a viral vector in large animals to treat congenital blindness	Defne Amado	20	Science translational medicine	2010

retinitis pigmentosa, macular degeneration, retinal pigment epithelium, retinal ganglion cell, retinal degeneration, and photoreceptor. Therefore, we further investigated the specific direction of gene therapy distribution in ophthalmology.

3.7. The focus of gene therapy in ophthalmology

Gene therapy for ocular diseases can be divided into many aspects by the regions of treatment, such as conjunctiva, cornea, lens, choroid, retina, and optic nerve. In the present study, only original studies were included in the analysis, and documents about the effects of gene transfection on functions were excluded. As shown by Fig. 9A, research associated with retinal diseases accounts for the largest proportion (n = 283), with most focused on *RPE-65* gene-mediated inherited retinal dysfunctions. Target pathological processes of gene therapy are mainly inflammation/immune response, angiogenesis, and degeneration. The papers published on gene therapy in retinal diseases are shown by year in Fig. 9B, which indicates that publications on gene therapy in retinal diseases increased gradually over the period studied here. These findings suggest that the research entry point of gene therapy mainly focuses on retinal diseases.

A



B **Top 20 Keywords with the Strongest Citation Bursts**

Keywords	Year	Strength	Begin	End	2000 - 2022
gene transfer	2001	10.35	**2001**	2011	
in vivo	2000	8.02	**2001**	2005	
endothelial growth factor	2001	4.93	**2001**	2007	
epithelium derived factor	2002	7.46	**2002**	2012	
choroidal neovascularization	2002	5.47	**2002**	2012	
eye	2002	4.48	**2004**	2008	
transgene expression	2002	6.21	**2005**	2012	
delivery	2002	4.48	**2007**	2009	
therapy	2002	4.47	**2007**	2010	
visual cycle	2008	4.72	**2008**	2011	
congenital amaurosis	2008	6.87	**2011**	2013	
achromatopsia	2010	6.52	**2012**	2015	
visual function	2011	4.79	**2014**	2020	
stem cell	2004	6.99	**2015**	2017	
glaucoma	2004	5.28	**2016**	2017	
macular degeneration	2004	5.33	**2017**	2019	
subretinal injection	2012	4.51	**2017**	2019	
gene editing	2016	4.87	**2018**	2022	
cell therapy	2017	6.86	**2019**	2022	
retinal dystrophy	2013	6.68	**2020**	2022	

Fig. 8. Network diagram on gene therapy keywords. (A) A visual map of keywords used at least 30 times. (B) Top 20 keywords with the strongest citation bursts by year.

4. Discussion

According to Gene Therapy Clinical Trials Worldwide Database, cancer diseases account for 68.2% (2513/3685) of global gene therapy clinical trials, and ocular diseases occupy only 1.5% (56/3685) of these [26]. Nevertheless, gene therapy remains to be important in ophthalmic research. Many hereditary ocular or systematic diseases caused by genetic defects can result in corresponding eye symptoms, such as X-linked retinoschisis [27], retinitis pigmentosa [28], and congenital cataract [29]. These cannot be rescued by

Table 6
Top 20 most frequently used keywords in papers on gene therapy in ophthalmology.

Rank	Keyword	Counts	Rank	Keyword	Counts
1	gene therapy	618	11	retinal pigment epithelium	109
2	animal model	315	12	stem cell	105
3	viral vector	305	13	retinal ganglion cell	101
4	in vivo	207	14	therapy	97
5	congenital amaurosis	186	15	retinal degeneration	90
6	retinitis pigmentosa	167	16	photoreceptor	83
7	delivery	167	17	visual acuity	72
8	expression	141	18	nanoparticle	65
9	mutation	122	19	transduction	64
10	macular degeneration	120	20	choroidal neovascularization	61

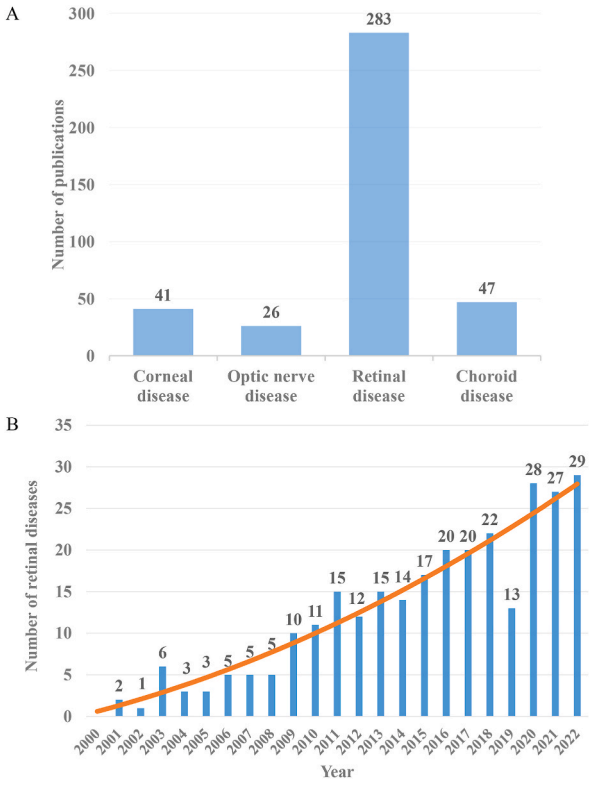


Fig. 9. The focus of gene therapy in ophthalmology. (A) Total numbers of publications on gene therapy for corneal disease, optic nerve disease, retinal disease and choroid disease from 2000 to 2022. (B) Annual original researches of retinal diseases in gene therapy from 2000 to 2022.

traditional drugs, so innovative treatment ideas, gene therapy being one example, are needed to correct pathological changes and clinical manifestations caused by gene defects [30,31]. Moreover, a small enclosed environment such as the eye facilitates gene therapy by allowing lower drug dosage and easier observation. This bibliometric analysis analyzed the development of gene therapy in ophthalmology from 2000 to 2022, and overviewed the evolution and frontiers in this promising field.

In general, publications on gene therapy in ophthalmology have increased gradually from 2000 to 2022. As the country with the largest number of clinical trials on gene therapy, the USA is the main source of the top 10 publishing institutions, which suggests their important contributions to this field. China, the USA and the UK are the top 3 countries in terms of gene therapy clinical trials and publications on gene therapy in ophthalmology. Multiple cooperation networks are formed among different countries and institutions, demonstrating that the value of gene therapy in ophthalmic diseases is constantly being explored and confirmed, and that more ocular genetic diseases will be alleviated or even cured in the future.

Among the top 10 cited or co-cited journals, the first ranked journal *Investigative Ophthalmology & Visual Science* is a leading journal for ophthalmic and vision research that has great reputation in the field. The highest number of gene therapy related ophthalmic studies published in ophthalmology specialty journals and general journals is comparable, which provides a broader perspective for the selection of subsequent journal submissions. The main focus of journals is on molecular aspects, genetics, biology, and ophthalmology.

Clinical trials play a key role in the discovery of new therapeutic strategies, advancing science, and changing clinical practice on the broadest possible scale [32,33]. Two of the strongest references were on LCA, currently in clinical use [34]. The two papers that have continued to be of high interest through 2022 both describe phase I clinical trials. One was on Leber's hereditary optic neuropathy (LHON) and showed no serious safety concerns after treatment with AAV to normally express the ND4 complementary DNA in patients with G11778A genotype LHOH [35]. The other was applied in inherited retinal dystrophy and showed no significant adverse effects after contralateral eye treatment with the AAV vector containing the *RPE65* gene [30], suggesting that the success of the first step can be followed by subsequent clinical trials.

The top 10 cited papers are all clinical trials. This is probably because the ultimate goal of the technology is for potential clinical treatment in patients with ocular diseases. Nine of the top 10 cited references are related to LCA. LCA is a group of hereditary blinding diseases caused by the *RPE65* mutation, and featuring severe damage to vision in children [36]. The most cited article describes a phase III clinical trial and shows that voretigene neparvovec gene replacement changes functional vision in *RPE65*-mediated inherited retinal dystrophy [13]. This has brought great encouragement to the development of gene therapy, promoting increasing research on gene therapy in ophthalmology.

The top 10 co-cited papers were published before 2010. Almost all of them described experimental studies and the main animal models used were dogs and mice. Most of the publications were related to AAV. AAV vector discovery saves gene therapy from failed clinical trials, and breakthroughs in gene therapy depend on more advanced science and technologies [37].

Keywords are the most concise words or phrases that describe the topic of an article and are widely used in document classification and publication retrieval [38]. The latest keyword with the strongest citation bursts is retinal dystrophy. This may be related to the approval of Luxturna, which is the first gene therapy drug approved for LCA [34, 39], provides encouragement for gene therapy in ophthalmology, and has stimulated interest in research on numerous gene therapy agents for inherited retinal diseases. Further exploration also confirmed that the retina is the most studied site and has largely maintained an upward research trend, ahead of several other popular areas of ophthalmic research, such as corneal diseases, optic nerve diseases, and choroid diseases. In addition, gene therapy treats diseases by transferring new genes to the patient's cells [3], thus it is closely linked to cell therapy. Keyword gene editing is a new strategy in gene therapy, for gene replacement, gene silencing, and gene addition [40]. Keyword subretinal injection is the preferred gene therapy delivery technique [16,41]. Keyword macular degeneration is a blinding eye disease with complex mechanisms. Sustained delivery of anti-angiogenic proteins through gene therapy approaches is a new therapeutic tool for the disease [10]. As shown in Table 6, we summarized the most important keywords with the highest frequency. On the other hand, in Fig. 8B, the results demonstrated the trend of keyword decline or rise, which indicates the correlation between keywords and time, and the strength of the correlation.

Although genetic variations do exist in diseases and some achievements have been made in recent years through targeted gene therapy, it is undeniable that gene therapy still has certain limitations, especially in implementation measures. These include ensuring an effective delivery process, treatment outcomes that do not meet expectations, cost, and complexity [42]. Secondly, an essential criterion to satisfy Luxturna treatment is the demonstration of a double allele pathogenic variant in *RPE65*, but variants of uncertain significance are increasingly available, such as *RPE65* C330T which has little effect on *RPE65* isomerization activity. In this case, we may not be able to gain significant benefits from gene therapies [43,44]. And then, there are severe adaptation delays after gene therapy. Lastly, invasive treatment (such as intraocular injection) is usually necessary for ocular gene therapies, thus, additional risks might be increased inducing complications such as foveal thinning, macular holes, endophthalmitis, and retinal detachment [34,45,46]. Therefore, it is still needed to further explore the effectiveness and safety of the application of ocular gene therapies.

5. Conclusion

The present study summarizes general characteristics in terms of countries, institutions, authors, journals, references, and directions of research on gene therapy in ophthalmology. We show that the overall publication trend from 2000 to 2022 is upward, the USA and the UK are the two main sources of publications. Close cooperation networks among countries, institutions, and authors have been formed globally. Furthermore, gene therapy research in ocular diseases primarily focuses on retinal dysfunctions, such as LCA and retinitis pigmentosa. Future progress of ocular gene therapy may retain this focus due to the pathogenesis of these diseases. Moreover, cornea and choroid diseases remain the major causes of irreversible blindness, which may be another research highlight in the future. The results of the study overview the past research in ocular gene therapies, and identify new perspectives for future research in this field.

Author contribution statement

Bingyan Li, Wei Tan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Zicong Wang, Haixiang Zhou, Jingling Zou: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Yun Li, Shigeo Yoshida: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Yedi Zhou: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Corresponding author serves as an advisory board member of Heliyon-Yedi Zhou.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18228.

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