• Bibliometric Research •

Publication trends of Leber congenital amaurosis researches: a bibliometric study during 2002-2022

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Abstract

● **AIM:** To analyze the changes in scientific output relating to Leber congenital amaurosis (LCA) and forecast the study trends in this field.

● **METHODS:** All of the publications in the field of LCA from 2002 to 2022 were collected from Web of Science (WOS) database. We analyzed the quantity (number of publications), quality (citation and H-index) and development trends (relative research interest, RRI) of published LCA research over the last two decades. Moreover, VOSviewer software was applied to define the co-occurrence network of keywords in this field.

● **RESULTS:** A total of 2158 publications were ultimately examined. We found that the focus on LCA kept rising and peaked in 2015 and 2018, which is consistent with the development trend of gene therapy. The USA has contributed most to this field with 1162 publications, 56 674 citations and the highest H-index value (116). The keywords analysis was divided into five clusters to show the hotspots in the field of LCA, namely mechanism-related, genotype-related, local phenotype-related, system phenotype-related, and therapy-related. We also identified gene therapy and anti-retinal degeneration therapy as a major focus in recent years.

● **CONCLUSION:** Our study illustrates historical research process and future development trends in LCA field. This may help to guide the orientation for further clinical diagnosis, treatment and scientific research.

● **KEYWORDS:** VOSviewer; bibliometrics; Leber congenital amaurosis; gene therapy; hotpots
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INTRODUCTION

Leber congenital amaurosis (LCA) is one of earliest and most severe form of inherited retinal dystrophies (IRD), resulting in degeneration of cones and rods or retinal pigment epithelial cells[1], which is responsible for 20% of school-age children blindness[2-3]. The clinical manifestations of LCA are heterogeneous, including early/congenital onset of vision loss, nystagmus, and amaurotic pupils, electrophysical manifestations such as non-detectable full field electroretinogram, and fundoscopic imaging like peripheral pigmentary retinopathy, frank macular atrophy, paleness and atrophy of optic disc, and vascular attenuation[4].

Diverse clinical features and individual heterogeneity of LCA may be related to genetic heterogeneity. To date, mutations in 25 genes have been identified as pathogenic genes of LCA, while other LCA-related genes and accompanied pathogenesis remain controversial and require further identification and studies[5-6]. In addition, there are challenges with current LCA treatments as well. So far, the first *RPE65* gene therapy drug Luxturna was approved by American food and drug administration, and several clinical trials related

to gene *RPE65* and *CEP290* have been completed or are in progress[7-8]. Nevertheless, there are still obstacles to overcome in the transformation of LCA gene therapy from fundamental science advances to clinical development[9]. This includes but is not limited to short-term follow-up and small sample trials, variability in patient response, safety of re-administration and surgical complications including effusion, subconjunctival hemorrhage, macular hole and increased intraocular pressure[10].

In view of the issues mentioned above, a comprehensive review of all existing LCA-related publications is urgently needed. Capability to analyze huge amounts of publications both qualitatively and quantitatively, to emphasize the relationships between published works, and predict academic development in a certain field has made bibliometrics one of such approaches[11-13]. Citation index, was first put forward by Gaifield[14] as a new approach to subject control of the literature of science". Subsequently bibliometric was formally defined by Pritchard[15], as "the application of mathematical and statistical methods to books and other media of communication".

Bibliometrics has experienced an explosive development in ophthalmic medical research. Nevertheless, as one of the hereditary retinal diseases with early onset and complex mechanism, the related research on LCA has not been carried out yet[16]. In order to best analyze the publications as a whole and the relationship between different researches in the LCA field, systematic literature review studies in this field are necessary. Through a comprehensive review of the research status in this field, we have identified the research hotspots and publication trends of LCA in the past 20y, and predicted the future development direction of this field, which will provide a deeper understanding of LCA.

MATERIALS AND METHODS

Search Strategy We conducted all searches on February 10th, 2023 in the Web of Science Core Collection (WOSCC), which was considered most suitable for bibliometric analysis, for publication retrieval and analysis. The keyword was "TS=Leber Congenital Amaurosis", "(TS= (Leber Congenital Amaurosis)) AND TS= (gene therapy)". Since *RPE65* is one of the LCA-related mutated genes that was studied earlier and entered clinical transformation, we set the keyword "(TS= (RPE65)) AND TS= (gene therapy)". All the publications with keywords in titles, abstracts, author keywords were included. The timespan of publications was set from 2002-01-01 to 2022-12-31 (publication date).

A total of 3427 publications were retrieved through WOSCC database. And 1229 non-core collection publications were excluded according to the database type. Forty non-Science Citation Index Expanded publications were excluded. Finally, 2158 publications were identified. A total of 2158 publications of "Leber Congenital Amaurosis", 921 publications of "Leber Congenital Amaurosis AND gene therapy", and 567 publications of "RPE65 AND gene therapy".

Data Collection Web of Science (WOS) was used for data extraction and analysis of publication information to understand the distribution of publication numbers, years, countries and regions, journals, institutions, and authors. The "Citation Report" function of WOS was applied to evaluate citation rates and H-index. Then, VOSviewer (Leiden University, Leiden, the Netherlands) and Microsoft Excel 2010 were used for bibliometric analysis and visualization of keywords network. GraphPad Prism 8.0.0 (131) was used to input and analyze data.

Bibliometric Analysis We used Microsoft Excel 2010 and GraphPad Prism 8.0.0 (131) to analyze and calculate the descriptive indexes exacted from WOS. Microsoft Excel 2010 was used to generate the modeling matching curve of publication trend. The prediction model is based on the formula: $f(x)=ax3+bx2+cx+d$, in which x represents the year and f(x) represents the cumulative number of publications. H-index is defined as a scholar/country has published H literatures, each of which has been cited at least H times in other publications, which is used to evaluate the academic influence of the scholar/country. Impact factor is derived from the latest version of Journal Citation Reports. Relative research interest (RRI) was obtained by calculating the ratio between the number of publications in a field and the number of publications in all fields each year, which partially reflect the level of worldwide interest in this field. VOSviewer is considered to be the appropriate approach for correlation analysis of keywords with high frequency in cited references which were provided by WOS. Furthermore, it can visualize keyword networks in the form of color-coded clusters that are classified on the basis of co-occurrence analysis. The novelty of keywords was evaluated by average appearing year.

RESULTS

Citation Count and H-index According to the WOS citation report, a total of 2158 LCA-related publications received a total of 83 119 relevant citations since 2002, with 58 766 citations without self-citations. From 2002 to 2022, each paper was cited an average of 38.52 times, among which the USA made the most contribution on citations (56 674, 46 759 without self-citations) and H-index (116; Figure 1A). England ranked the second in both citations and H-index (13 737 citations, 12 952 without self-citations, H-index 60) while Germany ranked the third on the H-index (9857 citations, 9403 without self-citations, H-index 56).

Contributing Countries and Publication Years Over the past 20y, the total number of LCA publications has generally increased year by year, with two peaks in 2015 and 2018 (161 publications in 2015, 164 publications in 2018; Figure 1B).

From 2002 to 2022, the greatest contribution was made by the USA with the most publications (1162, 53.8%), accounting for more than half of the total, followed by England (285, 13.2%) and Germany (215, 10.0%; Figure 1A). The USA also published most papers publications each year from 2002 to 2022 (Figure 1B), and peaked in 2015 and 2018 with 93 and 86 publications respectively. The number of publications related to LCA also increased significantly in England and Germany. In addition, RRI has increased from 0.003% in 2001 to 0.007% in 2018 and 0.008% in 2015, indicating an overall increase in global interest in this field over the last 20y, with peaks in 2015 and 2018.

Publication Trends and Predictions Overall, the publication rates on LCA have continued to rise over the past 20y, and predictions of publication trends for the next five years indicate that this growth continues (Figure 2A). Compared to other countries, the USA will remain the largest contributor of LCA publications and maintain a steady growth, both England and Germany have shown an increasing trend in the number of publications, but England has increased faster (Figure 2B-2F). It is worth mentioning that China has maintained the fastest growth rate in the number of publications since 2005 and is expected to exceed 200 LCA-related publications in the next five years (Figure 2F).

Contributing Institutions of Regions and Publishing Journals We searched the top 20 institutions with most LCA-related publications and found that the University of Pennsylvania contributed most papers to this field (224, 10.38%), followed by Pennsylvania Medicine (184, 8.53%). The University of London ranked the third (177, 8.20%), and the University College London ranked the fourth (175, 8.11%; Figure 3A).

We searched the top 20 publications contributing to this field, we found that more than 50% publications on LCA were included in the same 20 journals. *Investigative Ophthalmology and Visual Science* published most papers in this field with 303 (14.04%) publications, which was 5-10 times the number of other journals. *Molecular Vision* was the second-most contributor in this field with 82 (3.80%) publications over the past 20 years (Figure 3B).

Highly Cited Papers on Leber Congenital Amaurosis The most cited 10 papers in total are listed in Table 1[17-26] and the 2 papers with the most citations were both published in *New England Journal of Medicine*, a classic and authoritative medical periodical, and were both with the topic of gene therapy of LCA in 2008. The first was called Safety and efficacy of gene transfer for Leber's congenital amaurosis. The corresponding author was Bennett J. The second was called Effect of gene therapy on visual function in Leber's congenital amaurosis with the corresponding author Ali, Robin R.

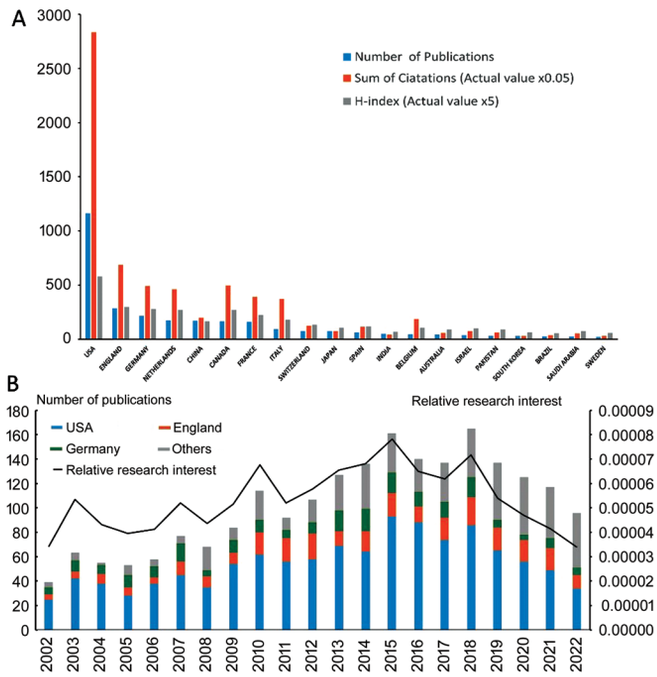

Figure 1 The number of publications and contributions on LCA in different countries/regions from 2002-2022 A: Top 20 countries/regions in the LCA publications. The blue bar represented the number of publications, orange bar represented the total sum of citations (actual value multiply by 0.05), gray bar represented the H-index (actual value multiply by 5). B: The RRI and proportion of the USA, England, Germany and others of each year in the field of LCA. The left axis showed the number publications, while the right axis showed the RRI. LCA: Leber congenital amaurosis; RRI: Relative research interest.

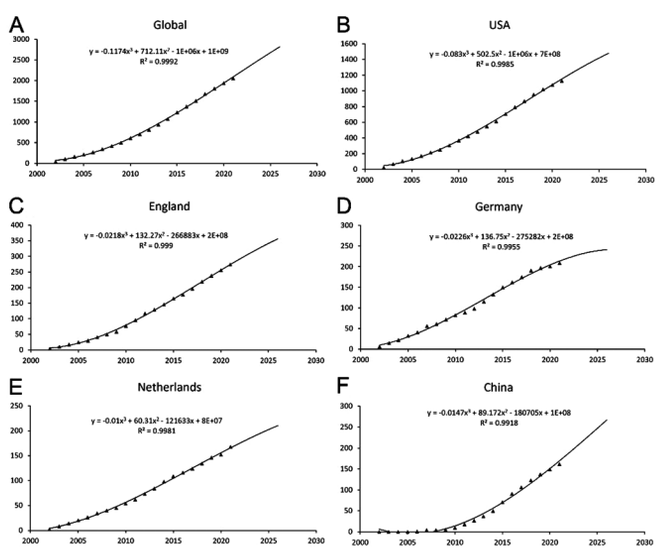

Figure 2 The publication growth trends of over the past 20y and prediction curve (determination coefficient R^2>0.99) A: Global; B: the USA; C: England; D: Germany; E: Netherlands; F: China.

Contributing Authors The top 10 authors contributing to this field according to the number of their publications and citations was displayed in Table 2. A total of seven of them were from the USA, two were from Netherlands, and one was from Canada. Four of them were from the University of Pennsylvania. The

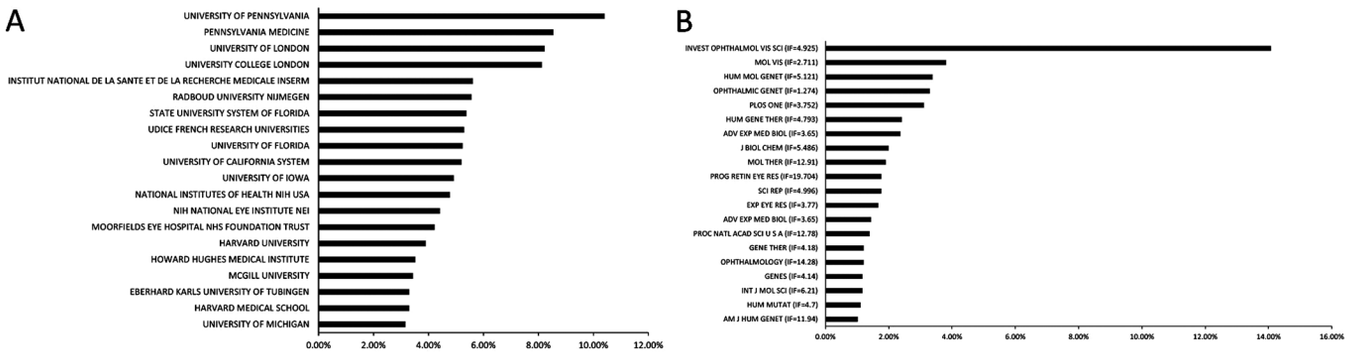

Figure 3 Academic journals and institutions for LCA papers A: Top 20 institutions around the world published most in the field of LCA; B: Top 20 journals ranked by the number of publications. LCA: Leber congenital amaurosis.

Table 1 Top 10 most cited papers in LCA research

Title	Coresponding authors	Journal	Publication year	Total citations
Safety and efficacy of gene transfer for Leber's congenital amaurosis[17]	Bennett, J.	*NEW ENGLAND JOURNAL OF MEDICINE*	2008	1601
Effect of gene therapy on visual function in Leber's congenital amaurosis[18]	Ali, Robin R.	*NEW ENGLAND JOURNAL OF MEDICINE*	2008	1487
Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial[19]	Russell, Stephen	*LANCET*	2017	830
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[20]	Jacobson, Samuel G.	*HUMAN GENE THERAPY*	2008	730
Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges[21]	High, Katherine A.	*NATURE REVIEWS GENETICS*	2011	684
Genes and molecular pathways underpinning ciliopathies[22]	Leroux, Michel R.	*NATURE REVIEWS MOLECULAR CELL BIOLOGY*	2017	664
Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial[23]	Bennett, J.	*LANCET*	2009	627
Leber congenital amaurosis: genes, proteins and disease mechanisms[24]	Cremers, Frans P.M.	*PROGRESS IN RETINAL AND EYE RESEARCH*	2008	574
Retinitis pigmentosa[25]	Hamel, C.	*ORPHANET JOURNAL OF RARE DISEASES*	2006	560
Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics[26]	Cideciyan, Artur V.	*PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*	2008	547

LCA: Leber congenital amaurosis.

Table 2 Top 10 most published authors in the LCA field

Author	Country	Affiliation	No. of publications	No. of citations
Jacobson S.G.	USA	UNIVERSITY OF PENNSYLVANIA	111	8088
Cideciyan A.V.	USA	UNIVERSITY OF PENNSYLVANIA	88	6951
Cremers F.P.M.	NETHERLANDS	RADBOUD UNIVERSITY NIJMEGEN	84	5124
Hauswirth W.W.	USA	UNIVERSITY OF FLORIDA	81	6596
Koenekoop R.K.	CANADA	MCGILL UNIVERSITY	68	4473
Stone E.M.	USA	UNIVERSITY OF IOWA	63	4247
Bennett J.	USA	UNIVERSITY OF PENNSYLVANIA	57	7107
Den Hollander A.I.	NETHERLANDS	RADBOUD UNIVERSITY NIJMEGEN	57	4761
Aleman T.S.	USA	UNIVERSITY OF PENNSYLVANIA	54	5441
Palczewski K.	USA	CASE WESTERN RESERVE UNIVERSITY	54	3638

LCA: Leber congenital amaurosis.

top 10 authors published 717 papers in total, which accounted for 33.2% of the total publications over the last 20y. Jacobson S.G. from the University of Pennsylvania published most papers from 2002 to 2022, with 111 publications and 8088 citations in total, followed by Cideciyan A.V. from the same institution, with 88 publications and 6951 citations.

Topic of Interest and Scientific Content Changes In LCA From 2002-2022 Keyword analysis was used to identify the most frequently occurring words and their correlations in the field of LCA research. The VOSviewer was applied to analyze the keywords which appeared more than 23 times in 2158 publications. A total of 101 keywords were obtained by

merging repeated words and excluding meaningless words, which could be divided into five main clusters according to co-occurrence frequency (Figure 4A), namely the mechanism-related cluster, the genotype-related cluster, the local phenotype-related cluster, the system phenotype-related cluster, and the therapy-related cluster. And with the growth of the year, the frequency of different keywords also changed (Figure 4B). For example, from 2011 to 2016, the high-frequency keywords of LCA-related studies have changed from "gene", "photoreceptor degeneration", which are related to LCA pathogenesis, to the establishment of animal models of LCA, such as "mouse model", "canine model", and then the initial exploration of gene therapy, such as "adeno-associated virus", to the evaluation of the safety of LCA-related clinical trials and the follow-up of patients' family genetics, such as "safety", "diagnosis", and "families".

In order to further explore the changes in the content of LCA scientific research over the past two decades, we presented more details of the information related to the most-cited articles per year from 2002 to 2022. The trend of scientific content in LCA with years is similar to Figure 4B. The representative articles included "Leber congenital amaurosis: Comprehensive survey of the genetic heterogeneity, refinement of the clinical definition, and genotype-phenotype correlations as a strategy for molecular diagnosis" in 2004, which reported a comprehensive mutational analysis of the all known genes in 179 unrelated LCA patients and searched for phenotype variations; and "Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial" in 2017, which performed the phase 3 trial to assess the effect of AAV2-hRPE65v2 gene therapy on inherited retinal dystrophy (ClinicalTrials.gov number, NCT00999609).

Publication Year of LCA Gene Therapy Over the past 20y, the number of publications related to LCA gene therapy has shown a steady increase generally, with two peaks in 2015 and 2018 which was roughly consistent with the publication timing trend of LCA papers as shown in Figure 1. In addition, the number of published articles related to gene therapy of *RPE65*, the representative mutant gene of LCA, also showed a gradually increasing trend, and reached a peak around 2015 and 2018. The USA published the most papers related to gene therapy per year from 2002 to 2022, peaking around 2015 and 2018 with 45 and 46 publications (Figure 5).

DISCUSSION

This paper evaluated the research frontiers and hotpots and forecasted the future development trends in LCA-related studies. The global interest in this field increased over the last 20y, with peaks in 2015 and 2018. The USA made the most contribution in the field of LCA research, with 1162 publications, 56 674 citations and the highest H-index value, 116. The keywords related to LCA were classified into five groups: mechanism-related cluster, genotype-related cluster, local phenotype-related cluster, system phenotype-related cluster, and therapy related cluster. We also identified gene therapy and retinal regeneration therapy as a major focus in recent years.

In the analysis of the contributions of various countries and regions in the field of LCA, our study showed that by far, most studies on LCA came from the USA, followed by England and Germany, which was inseparable from the higher prevalence of LCA in America and Europe. Garanto *et al*[27] and Stepanova *et al*[28] indicated that the population frequency of LCA was approximately 1 in 3000 to 50 000 in North America and Europe, and seemed to be increasing, compared to the global prevalence of 1/81 000[29]. Moreover, mutations in *CEP290*, *GUCY2D* and *RPE65*, which account for a higher proportion of LCA, are generally more common in Caucasian populations than in other ethnic groups[30-32], which revealed regional differences in the genetic backgrounds of LCA cases. In addition, with the priority development of genomics, high-throughput sequencing and other technologies in the USA as well as the new concepts and approaches it spawned, LCA-related genes and variants have been gradually discovered, and the number of related studies on LCA subtypes with defined molecular genetic causes also increased at the fastest speed with the help of The American College of Medical Genetics and Genomics (ACMG)[33]. The USA started research on LCA earlier than other countries and regions, and has maintained a leading position in all aspects for nearly 20y. It is worth noting that China has maintained the fastest growth rate since the LCA study began in 2006. Meanwhile, the researches of other countries and regions also played a very important role in the field of LCA as well.

In the study of LCA, we were able to identify the institutions and authors most likely to guide future orientation and their academic influence in the field of LCA with the help of citation number and H-index[34-35]. According to our results, the USA researchers published most papers, with the most citations and the highest H-index, and would continue to make important contributions in the field of LCA in the future. It is worth noting that although China ranked the fifth and maintained the fastest growth rate in the number of publications since 2005, it has fewer citations and lower H-index than Netherlands and even Canada, which ranked the fifth and sixth in the number of publications. This might be due to the imbalanced development and research capacity of Chinese hospitals in different regions, as well as the imperfect follow-up system and electronic medical records.

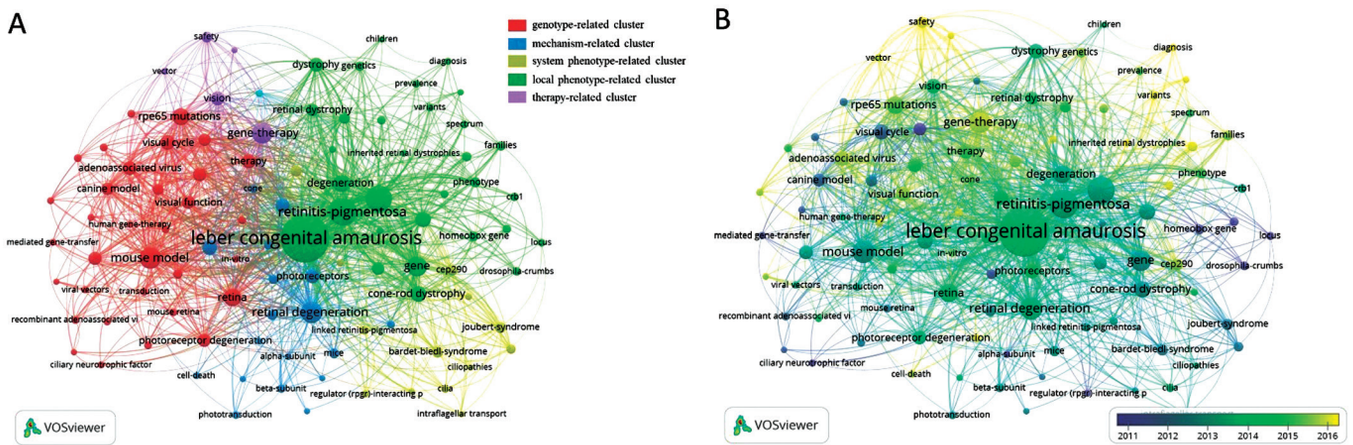

Figure 4 Keywords analysis by VOSviewer A: Keywords were divided into five clusters by co-occurrence frequency, including genotype-related cluster (red), mechanism-related cluster (blue), system phenotype-related cluster (yellow), local phenotype-related cluster (green), and therapy-related cluster (purple); B: All the keywords were color-coded by the average number of occurrences. Blue words appeared earlier, and yellow words appeared more recent.

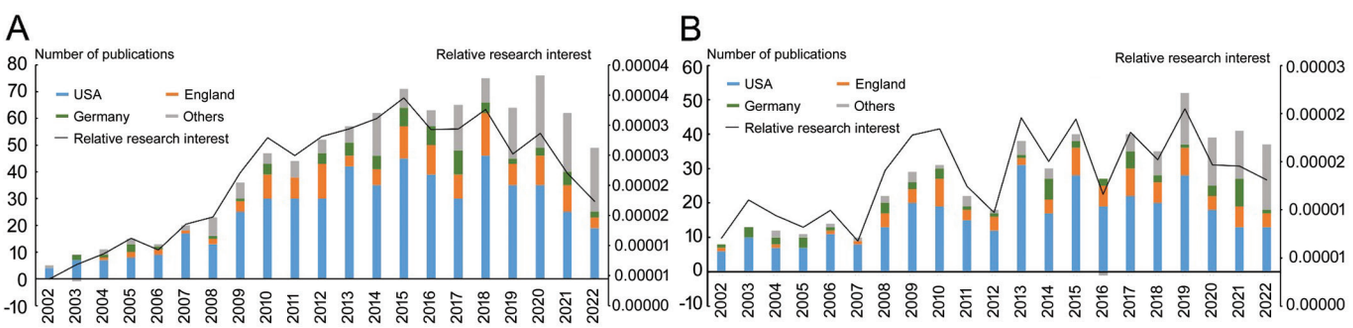

Figure 5 The number of publications and contributions on gene therapy for LCA in different countries/regions from 2002-2022 A: The RRI and proportion of the US, England, Germany and others of each year with the keywords "(TS=(Leber Congenital Amaurosis)) AND TS=(gene therapy)". The left axis showed the number publications, while the right axis showed the RRI. B: The RRI and proportion of the US, England, Germany and others of each year with the keywords "(TS=(RPE65)) AND TS=(gene therapy)". The left axis showed the number publications, while the right axis showed the RRI. LCA: Leber congenital amaurosis; RRI: Relative research interest.

On the whole, the volume of literature published in the field of LCA and its have shown an increasing trend in the past 20y, with the peaks appearing in 2015 and 2018, and have fallen in recent years. This may due to the development trend related to the advances of theoretical basis and clinical transformation of gene therapy. The establishment of canine model of RPE65-mutated LCA in 1998[36], and the application of it for preclinical studies in 2001[37] laid the foundation for the rapid development of gene therapy over the next two decades. Then the feasibility and safety of gene augmentation therapy represented by adeno-associated virus (AAV) in the treatment of LCA were reported[38]. Subsequently, several clinical trials of gene therapy for LCA were conducted, such as AAV2-hRPE65v2, rAAV2-CBSB-hRPE65, and rAAV2/2.hRPE65p.hRPE65[9,39]. By 2015, it was reported that visual gains could be detected and last for at least 3y, but a diminution of visual sensitivity caused by photoreceptor degeneration was also found in long-term follow-up[40-41], which promoted the next stage of gene therapy in clinical research. In 2017, after the first ophthalmic gene therapy (Luxturna, AAV2-hRPE65v2) was approved, phase III trials of efficacy and safety of AAV2-hRPE65v2 in patients with *RPE65*-mediated LCA was completed[5]. However, given the complexity and heterogeneity of virulence genes in LCA patients, the adaptive potential of gene therapy is limited[42]. These results mean that the global interest in LCA is relevant to the development of gene therapy. In the early stage, the gathering momentum of gene therapy brought vigorous vitality to the field of LCA, and the number of all kinds of research increased by an explosion. The growth rate of LCA research gradually stabilized as questions about the long-term safety and efficacy of the treatment emerged. The proper solution of such problems is expected to bring new peaks to the research in this field.

The keywords analysis indicated that retinal degeneration has been the core word that mainly described the pathogenesis of LCA. LCA subtypes caused by different mutated genes also show a diversity of mechanisms. These wide-ranging mutations are involved in different aspects of maintaining normal

retinal function or health such as phototransduction (*AIPL1*, *GUCY2D*, *RD3*), signal transduction (*CABP4*, *KCNJ13*), photoreceptor morphogenesis (*CRB1*, *CRX*, *GDF6*, *PRPH2*), ciliary transport disorders (*CEP290*, *RPGRIP1*, *LCA5*, *IQCB1*, *SPATA7*, *TULP1*), retinoid cycle (*LRAT*, *RDH12*, *RPE65*), retinal differentiation (*OTX2*), guanine synthesis (*IMPDH1*), and coenzyme NAD biosynthesis (*NMNAT1*)[43-44].

Gene therapy is a compelling approach due to the single-gene pathological nature of most LCAs, and retina is a favorable target for managing genetic vectors due to its superior immune environment and multiple methods for assessing sensitivity and function[39]. Therefore, the hotpots of LCA research have shifted from the pathogenesis to the treatment especially the gene therapy and its clinical trials of LCA in recent years as color coded keywords indicated. At present, several clinical trials related to *RPE65* and *CEP290* have been registered by multiple institutions and are in various phases. Although AAV is the most widely used technique for gene therapy in LCA, other techniques such as RNA-based antisense oligonucleotide therapy, gene editing therapy and 11-cis-retinal replacement have also gained wide attention in recent years[9]. The application of CRISPR/Cas9-mediated genome editing technology in LCA2 and LCA10 emerged, which addressed issues such as the limited carrying capacity of AAV[45-46]. Moreover, QR-110, the best-performing antisense oligonucleotides designed to correct the splicing defect associated with mutation was confirmed to be effective in the treatment of LCA10 when used in retinal organoids because of its good retinal accessibility and good tolerability after intravitreal injection in humans[47]. In recent years, the safety of the treatment has subsequently been considered. The synthetic 9-cis-retinyl acetate QLT091001 can replace 11-cis-retinal which is missing in degenerative retina of LCA patients with RPE65 and LRAT defects. It binds to opsin to form the photoactive form required for the cascade of phototransduction, which preserves the morphology of retina[48]. As an oral treatment, it made up for the vacancy of non-invasive treatment for LCA. We believe the priority of future LCA researches are expected to lie in the investigation of more unexplored genes on the pathogenesis accompanied by the development and screening of related therapeutic targets. With such novel medication, it is then necessary for researches on long-term safety and effectiveness of multi-center marketed drugs for LCA patients, and the development of targeted and safely delivered drug carriers with higher editing efficiency which would benefit patients more.

There are also some limitations in our study. First, we only searched in WOS database, instead of Google Scholar and PubMed, which may lead to the missing of some publications. In addition, only English publications were included, which might partially bring bias to our results.

In conclusion, our study retrieved the published research on LCA and fully illustrated the topic of interest, research frontiers and publication trends in the field of LCA over the past two decades. At present, gene therapy is the top priority of LCA related research, and breaking through its limitations will become the future development direction. This study can help scientists understand the history and future development trend of LCA research and provide guidance for scientific research. It can help doctors appreciate the hotspots in this field and make better clinical decisions, as well. It may also guide future research trends on LCA.

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