Publication Trends of Leber Congenital Amaurosis Researches: A Bibliometric Study during 2002-2021

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Research Article

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Abstract

Objective

Leber Congenital Amaurosis (LCA) is one of earliest and most severe form of inherited retinal dystrophies. In this study, we aimed to analyze the changes in scientific output relating to LCA and forecast the study trends in this field.

Methods

All of the publications in the field of LCA from 2002 to 2021 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 2057 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 US has contributed most to this field with 1125 publications, 52970 citations and the highest H-index value, 112. 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.

Conclusions

Our study illustrated 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.

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]. The prevalence of LCA ranges from 1/81,000 to 1/30,000, accounting for 5% of all IRDs. It is also responsible for 20% of school-age children blindness [2–4]. 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 [5, 6].
The present of diversity of 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 [7,8]. In addition, there are challenges with current LCA treatments as well. Although the first RPE65 gene therapy drug Luxturna was approved by American food and drug administration (FDA) [9], and several clinical trials related to gene RPE65 and CEP290 have been completed or are in progress [10–12], there are still obstacles to overcome in the transformation of LCA gene therapy from fundamental science advances to clinical development [13], such as short-term follow-up and small sample trials, variability in patient response, surgical complications including effusion, subconjunctival hemorrhage, macular hole and increased intraocular pressure, and safety of readministration [14–16].

In view of the issues mentioned above, a comprehensive review of all existing LCA-related publications is urgently needed. Bibliometric analysis is the optimal tool to tackle this problem, which can report current topic of interest, and predict academic development in a certain field [17,18]. In this study, we identified the frontiers of the LCA research, delineated the publication trends over the past 20 years, and predicted the future development trend of this field, which will provide a deeper understanding of LCA research and is expected to guide the development orientation in the future.

**Methods**

**Search Strategy**

We used 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 [19], we set the keyword “(TS=(RPE65)) AND TS=(gene therapy)“. And all the publications with keywords in titles, abstracts, author keywords were included. The timespan of publications was set from 2002-01-01 to 2021-12-31 (publication date).

A total of 3228 literatures were retrieved through WOSCC database. 1050 non-core collection publications were excluded according to the database type. 121 non-Science Citation Index (SCI) Expanded publications were excluded. Finally, 2057 literatures were identified. A total of 2057 publications of “Leber Congenital Amaurosis”, 869 publications of “Leber Congenital Amaurosis AND gene therapy”, and 530 publications of “RPE65 AND gene therapy”.

**Data Collection**
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. The h-index could access the quantity and quality of academic output of researchers, and was collected from WOS database. relative research interest (RRI) was obtained by dividing the number of publications in a field by the number of publications in all fields, which partially reflect the level of worldwide interest in this field. The prediction model is \( f(x) = ax^3 + bx^2 + cx + d \), which was the matched curve generated from the cumulative publications. We used VOSviewer to build a keyword co-occurrence network based on titles and abstracts. Frequencies over 23 was the criteria of the exhibited keywords. And the novelty of keywords was evaluated by average appearing year (AAY).

**Results**

**Citation Count and H-Index**

According to the WOS citation report, a total of 2,057 LCA-related publications received a total of 76,784 relevant citations since 2002, with 54044 citations without self-citations. From 2002 to 2021, each paper was cited an average of 37.33 times, among which the US made the most contribution on citations (52970, 43520 without self-citations) and H-index (112) (Fig. 1A). England ranked second in both citations and H-index (12767 citations, 12031 without self-citations, H-index 59) while Germany ranked third on the H-index (9314 citations, 8870 without self-citations, H-index 54).

**Contributing Countries And Publication Years**

Over the past 20 years, the total number of LCA publications has generally increased year by year, with two peaks in 2015 and 2018 (161 publications in 2015, 165 publications in 2018) (Fig. 1B). From 2002 to 2021, the greatest contribution was made by the US with the most publications (1125, 54.7%), accounting for more than half of the total, followed by England (274, 13.3%) and Germany (209, 10.2%) (Fig. 1A). The US also published most papers publications each year from 2002 to 2021(Fig. 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, relative research interest (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 20 years, with peaks in 2015 and 2018.
**Publication Trends And Predictions**

Overall, the publication rates on LCA have continued to rise over the past 20 years, and predictions of publication trends for the next five years indicate that this growth continues (Fig. 2A). Compared to other countries, the USA will remain the largest contributor of LCA publications and maintain a steady growth, England shows a similar trend of sustained growth, while Germany will show a slowing down growth trend (Fig. 2B-F). 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 (Fig. 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 (216, 10.5%), followed by League of European Research (215, 10.45%). The University of London ranked third (171, 8.31%), and the University College London ranked fourth (169, 8.22%) (Fig. 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 Visual Science published most papers in this field with 295 (14.34) publications, which was 5–10 times the number of other journals. Molecular Vision was the second-most contributor in this field with 82 (3.99%) publications over the past 20 years (Fig. 3B).

**Highly Cited Papers On Lca**

The most cited 10 papers in total are listed in Table 1 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. 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.
<table>
<thead>
<tr>
<th>Title</th>
<th>Corresponding Authors</th>
<th>Journal</th>
<th>Publication Year</th>
<th>Total Citations</th>
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</thead>
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<tr>
<td>Safety and efficacy of gene transfer for Leber's congenital amaurosis</td>
<td>Bennett, J.</td>
<td>NEW ENGLAND JOURNAL OF MEDICINE</td>
<td>2008</td>
<td>1562</td>
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<td>Effect of gene therapy on visual function in Leber's congenital amaurosis</td>
<td>Ali, Robin R.</td>
<td>NEW ENGLAND JOURNAL OF MEDICINE</td>
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<td>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</td>
<td>Jacobson, Samuel G.</td>
<td>HUMAN GENE THERAPY</td>
<td>2008</td>
<td>715</td>
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<tr>
<td>Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial</td>
<td>Russell, Stephen</td>
<td>LANCET</td>
<td>2017</td>
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<td>Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges</td>
<td>High, Katherine A.</td>
<td>NATURE REVIEWS GENETICS</td>
<td>2011</td>
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<td>Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial</td>
<td>Bennett, J.</td>
<td>LANCET</td>
<td>2009</td>
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<td>Genes and molecular pathways underpinning ciliopathies</td>
<td>Leroux, Michel R.</td>
<td>NATURE REVIEWS MOLECULAR CELL BIOLOGY</td>
<td>2017</td>
<td>549</td>
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<tr>
<td>Leber congenital amaurosis: Genes, proteins and disease mechanisms</td>
<td>Cremers, Frans P.M.</td>
<td>PROGRESS IN RETINAL AND EYE RESEARCH</td>
<td>2008</td>
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<td>Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics</td>
<td>Cideciyan, Artur V.</td>
<td>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA</td>
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<td>Retinitis pigmentosa</td>
<td>Hamel, C.</td>
<td>ORPHANET JOURNAL OF RARE DISEASES</td>
<td>2006</td>
<td>513</td>
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</table>

**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 US, two were from Netherlands, and one was from Canada. Four of them were from the University of Pennsylvania. They published 703 papers, which accounted for 34.2% of the total publications over the last 20 years. Jacobson S.G. from the University of Pennsylvania published most papers from 2002 to 2021, with 108 publications and 7748 citations in total, followed by Cideciyan A.V. from the same institution, with 85 publications and 6657 citations.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Affiliation</th>
<th>No. of Publications</th>
<th>No. of Citations</th>
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<td>4061</td>
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<td>RADBOUD UNIVERSITY NIJMEGEN</td>
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<td>Bennett J.</td>
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<tr>
<td>Boye S.L.</td>
<td>USA</td>
<td>UNIVERSITY OF FLORIDA</td>
<td>52</td>
<td>4163</td>
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</table>

Topic Of Interest And Key Words

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 2057 publications. A total of 101 keywords were obtained by merging repeated words and excluding meaningless words, which could be divided into four main clusters according to co-occurrence frequency (Fig. 4), namely the mechanism-related cluster, the genotype-related cluster, the local phenotype-related cluster, the system phenotype-related cluster, and the therapy-related cluster.
Publication Year Of Lca Gene Therapy

Over the past 20 years, 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 Fig. 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 US published the most papers related to gene therapy per year from 2002 to 2021, peaking around 2015 and 2018 with 45 and 46 publications (Fig. 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 20 years, with peaks in 2015 and 2018. The US made the most contribution in the field of LCA research, with the most publications, most citations, the highest H-index, and the most cited author. And bibliometric analysis was applied to predict the publication trends of hotpots in the next few years. 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.

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 US, followed by the number of studies in England and Germany, which was inseparable from the higher prevalence of LCA in America and Europe. Garanto, A. et al. indicated that the population frequency of LCA was approximately 1 in 50,000 in North America and Europe [20], and seemed to be increasing, compared to the global prevalence of 1/81,000 [21]. 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 [22–24], 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 US 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) [25]. The US started research on LCA earlier than other countries and regions, and has maintained a leading position in all aspects for nearly 20 years. 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 in the field of LCA. Citation number and H-index can partially reflect the influence of specific researchers and institutions [26,27]. According to our results, the US 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 fifth and maintained the
fastest growth rate in the number of publications since 2005, it has fewer citations and lower H-index than Netherlands, which ranked fourth, and even Canada, which ranked 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. However, the quality of their research will continue to improve as many scientists and clinicians are aware of these issues and working on them.

Our study also suggested that Investigative Ophthalmology Visual Science, Molecular Vision and Human Molecular Genetics are the main journals of LCA publications, which means that future advances in LCA research are likely to continue to be published in these journals.

The number of publications in the field of LCA has been increasing year by year over the last 20 years, with two non-negligible peaks in 2015 and 2018 (161 publications in 2015, 165 publications in 2018). Similarly, the relative research interest (RRI), the index which represents global attention being paid to LCA, which shows the same pace of development (from 0.003–0.008%) (Fig. 1B. This trend is also closely related to the advances of theoretical basis and clinical transformation of gene therapy (Fig. 4A). The establishment of canine model of RPE65-mutated LCA in 1998 \[28\], and the application of it for preclinical studies in 2001 \[29\] 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 \[30\], and a number of clinical trials targeting RPE65 have been carried out. By 2008, three separate clinical trials conducted by University of Pennsylvania, University of Florida, and University of London all confirmed that the vector delivery (AAV2-hRPE65v2 vector, rAAV2-CBSB-hRPE65 vector and rAAV2/2.hRPE65p.hRPE65 vector) was safe and did not report any adverse events \[31–33\]. By 2015, clinical trials conducted by University of Pennsylvania and University of London indicated that visual gains could be detected and last for at least 3 years, but a diminution of visual sensitivity caused by photoreceptor degeneration was also found in long-term follow-up \[34,35\], which promoted the next stage of gene therapy in clinical research. In 2017, phase III trials of efficacy and safety of AAV2-hRPE65v2 in patients with RPE65-mediated LCA was completed \[10\], followed by FDA approval of the first gene therapy drug Luxturna (commercial name) targeting RPR65. Subsequently, the process of LCA-related gene discovery, preclinical studies with animal or cell models, cloning of genes into suitable vectors, and other related research has exploded and moved to the next stage.

Color coded keywords indicated that the hotpots of LCA research have shifted from the pathogenesis to the treatment especially the gene therapy of LCA in recent years. 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 \[13\]. 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 \[36,37\].
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. 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. As an oral treatment, it made up for the vacancy of non-invasive treatment for LCA.

The keywords analysis indicated that retinal degeneration has been the core word that mainly described the pathogenesis of LCA, which extends to the death and degeneration of photoreceptor mainly consisting of rod and cone cells. 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. Mutations in any gene associated with LCA will cause disruption of these functions 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 (NMMAT1). The pathological mechanisms caused by these specific gene mutations bring hope for the development of animal models for basic research and the development of gene therapy in clinical transformation.

There are also some limitations in our study. Only SCI database was included, which might lead to biased results. In addition, the most recent high-quality papers in our study could not be cited at the time when the data was collected, which might partially affect the 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. This study can help scientists and clinicians understand the history and future development trend of LCA research, and guide the orientation for further clinical diagnosis, treatment and scientific research.

**Declarations**

**Financial Disclosures:**

There are no financial conflicts of interest to disclose.

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Author Contributions:

XH, MZ, and XS conceived the bibliometric study. YW, MX and XZ were statistician and undertook the secondary analysis. YC, JC and SH checked the statistical methods and analysis results. XH, MZ and XS jointly drafted the manuscript, which was contributed to by YW and MX. All authors have read and agreed to the published version of the manuscript.

Consent for publication:

Not applicable.

Ethics approval and consent to participate:

Not applicable.

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

References


Figures

Figure 1
(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 relative research interest (RRI) and proportion of the US, 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.

Figure 2

The publication growth trends of over the past 20 years and prediction curve. (A) Global, (B) the US, (C) England, (D) Germany, (E) Netherlands, (F) China.
Figure 3

(A) Top 20 institutions around the world published most in the field of LCA. (B) Top 20 journals ranked by the number of publications.
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, yellow words appeared more recent.
Figure 5

(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.