Original Article

A bibliometric analysis of research on genetic retinal diseases done in India

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Purpose: To conduct a bibliometric analysis of research on genetic retinal diseases (GRD) done in India published from 2011 to 2020 in peer-reviewed journals, and assess the productivity, trends in journal choice, publication types, research funding, and collaborative research. **Methods:** We searched PubMed for articles indicating both vision-related content and author affiliation with an Indian research center. We identified research collaborations and classified articles as reporting basic science, clinical science, or clinically descriptive research. Impact factors were determined from Journal Citation Reports for 2015. **Results:** The total number of published articles that were retrieved from 2011 to 2021 was 341. During the 10 years of study, the annual output of research articles has nearly doubled, that is, from 21 in 2011 to 44 in 2021. A total of 298 (87%) articles were published in international journals, and 149 (42%) articles in vision-related journals had an impact factor. A total of 224 (65%) articles came from six major eye hospitals. Clinical science articles were most frequently (86%) published, whereas basic science was the least (14%). The diseases on which the maximum and the minimum number of articles were published were retinoblastoma (n = 82,24%) and Stargardt disease (n = 3, 0.9%), respectively. **Conclusion:** This bibliometric study provides a broad view of the current status and trends in the research on GRD done in India and may help clinicians, researchers, and policymakers to better understand this research field and predict its dynamic directions.

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Bibliometrics is an optimal choice to evaluate particular research trends concerning a certain field over time.[1] A systematic assessment of ophthalmology and vision-related research publication from India are very limited and particularly the analysis of the research on genetic retinal diseases (GRD) is not available. Without objective information about current research output, it is difficult to plan for necessary improvements in the infrastructure related to the understanding, treatment, and prevention of eye diseases. Thus, it is important to accurately assess the global and regional productivity of ongoing research on GRD. As per the World Health Organization (WHO), genetic eye disorders are one of the top 10 major causes of global ocular health burden. Age-related macular degeneration (AMD) and diabetic retinopathy (DR) take the major share of the adult eye diseases component that particularly affects the neurovascular retina.[2] More than 100 genes are known to cause Mendelian types of retinal degenerations including syndromic and non-syndromic retinitis pigmentosa (RP), and it is presumed that this constitutes only 60% of all the genes known so far, and the remaining are yet to be identified.[2] The burden of GRD in India is significant. Many significant genes including RPE65 have been identified from this region and are associated with consanguineous autosomal recessive pedigrees.[3]

The rates of different inherited retinal diseases vary.[4] Monogenic vitreoretinal diseases have a prevalence of 1 in 2,000 individuals.[4] The prevalence of RP is between 1 in 3,000 to 1 in 5,000 individuals.[4] Choroideremia has an incidence rate of 1 in 50,000.[4] Bardet–Biedl syndrome affects 1 in 1,20,000 Caucasians.[4] Both Joubert syndrome and Alagille syndrome have a prevalence rate of 1 in 1,00,000 individuals.[4]Mendelian diseases such as RP, congenital stationary night blindness (CSNB), and Stargardt disease have been reported to be caused by pathogenic genetic mutations, whereas adult-onset retinal diseases such as AMD and DR have been shown to be hereditary through family-based studies and have been associated with variations in genes involved in the disease pathways.[2]

The prevalence of AMD is 0.05% under age 50 years and 12% above age 80 years with a rising estimation of 196 million in 2020 to 288 million by 2040 and with a higher prevalence among Europeans compared to the Asians.[4,5] In India, the DR prevalence is around 15–18% among the diabetic population over 40 years of age[6] The prevalence of RP is 1 in 930 in urban South India, and 1 in 372 in rural India (≥40 years).[7] The reason for such a high prevalence of RP is not clear but could be due to consanguineous marital practice that is widely prevalent in some parts of India. Consanguinity adds to the proportion of autosomal recessive eye diseases in the Indian population.[8] Retinoblastoma represents 3% of all childhood cancers and is the most common intraocular malignancy of childhood.[9] Recent advances in the genetics of retinoblastoma have also helped in improving the overall clinical management of this malignancy.

This article reports the findings of publications on GRD by researchers in India. In addition to the standard bibliometric

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analyses, the results may help identify researchers with access to unique genetic populations, highlight opportunities for private and public funders to identify possible research facilities while helping researchers identify potential funders, and encourage collaborations beyond those already recognized.

Methods

This study examined the publications on GRD done by ophthalmologists and researchers working in India through a systematic search of Medline using the PubMed interface. GRD was defined as the disease of the retina having possible or definite genetic etiology.[2,3]

Records were retrieved using the search terms Gene OR Genetics AND a combination of natural language and MeSH (Medical Subject Headings) terms to retrieve a comprehensive set of articles in the field of retina diseases. Retrieval was restricted to publications the author was associated with an Indian institution using the "affiliation" field of the database.

The period of analysis was restricted to the publication from January 2011 to December 2020 by using the "limit" function.

The data were obtained from each citation PMID using PubMed to XL tool (https://pubmed2xl.com/xml/). The retrieved data were recorded in a spreadsheet, which included date of publication, author affiliation, publication type, journal title, and type of the article. The publications were divided according to those published in journals of ophthalmology specialty and journals of specialties other than ophthalmology. All articles included were examined for classification into one of three categories: "basic science" (investigative) if experiments were performed on animals or *in vitro*, "clinical science" (investigative) if experiments were done involving humans, or "clinically descriptive" for case presentations and articles that reviewed diseases. These categories of data were identified using "animals" and "humans" in the "limit" options in the database; the "publication type" limit function was used for retrieving clinically descriptive publications. Another important analysis, which was identifying collaborative research between Indian researchers and investigators from other countries, was done by using affiliation filed.

Results

Number of publications, types of publications, and years of publications

A total of 341 articles from 2011 to 2020 met the search criteria, including 247 original articles, 34 review articles, and 55 case reports. The trend of publications on GRD in India follows an exponential increase in the past 10 years [Fig. 1]. The number of publications has increased from 21 (2011) to 44 (2020), and almost 59% of them (n = 200) were published over the last 5 years of the study period. Of these 341 articles, 87% (n = 298) articles were published in journals published outside India and 13% (n = 43) articles were published in Indian journals. The journal-wise distribution shows 42% (146/341) of the articles were published in an ophthalmic journal and the highest number of articles were published in the Indian Journal of Ophthalmology (IJO) [Fig. 2]. The remaining 58% (195/341) articles were published in non-ophthalmic journals.

The number of published articles was considered as the quantity of research. The measure of the quality of the publication was based on the impact factor of the journal in which the article was published.[10] According to 2020 ophthalmology journals impact factors (except orbit journal), all articles were published in journals with impact factors [Fig. 2].

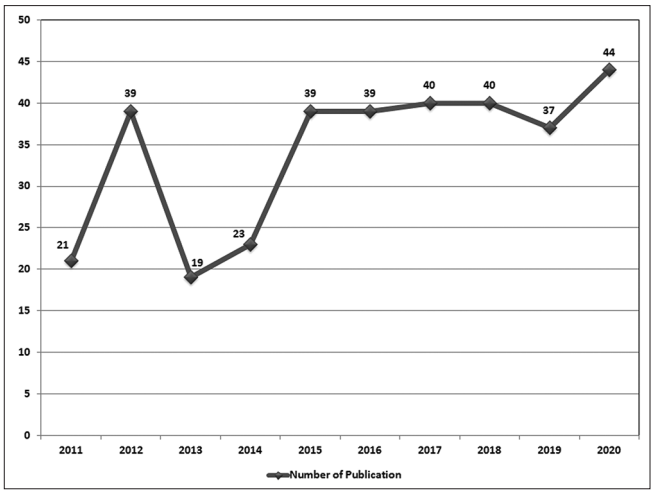

Figure 1: Year-wise trends in the number of publications

Using features of PubMed as described above, articles were classified as basic science, clinical science, or clinically descriptive. Overall results for the period under study showed that clinical science articles were consistently the largest percentage among the total articles published (n = 237, 70%), clinically descriptive articles were the second most prevalent (n = 56, 16%), and basic science comprised the smallest category (n = 48, 14%) [Fig. 3].

Institution-wise analysis

Six eye care institutions in India together have contributed to 65% of the share (with 224 articles) of the total number of publications. The maximum number of articles was from Sankara Nethralaya (SN) [Table 1].

In total, 2,448 authors' names were documented in publishing research on GRD, with an average of 7.1 authors per publication. A total of 184 articles were published by the top 10 authors, accounting for 35.7% of the total publications. Raman R of SN had published 29 papers, ranking first in the number of publications. Among the top 10 authors, 5 authors were from SN [Table 2].

Collaborative research

The range of collaborative research between Indian ophthalmic researchers and centers outside India was measured by the number of publications coming out of the collaboration. The highest number of publications were from collaboration with the USA (n = 36) [Table 3].

Diseases-wise publications

As per the disease-wise analysis, a greater number of articles were published on retinoblastoma (n = 82, 24%), DR (n = 78, 23%), AMD (n = 53, 15.5%), and RP (n = 50, 15%) [Table 4].

Discussion

This study looked at the research productivity of Indian ophthalmologists, and vision researchers on research on GRD. According to Sieving PC *et al.*, globally 21,316 articles were published on ocular genetics during 2000–2017.[10] The current study found a total of 12,077 articles published on GRD between 2011 and 2020. The United States accounted for 22% of publications (n = 2,632) and ranked first in the

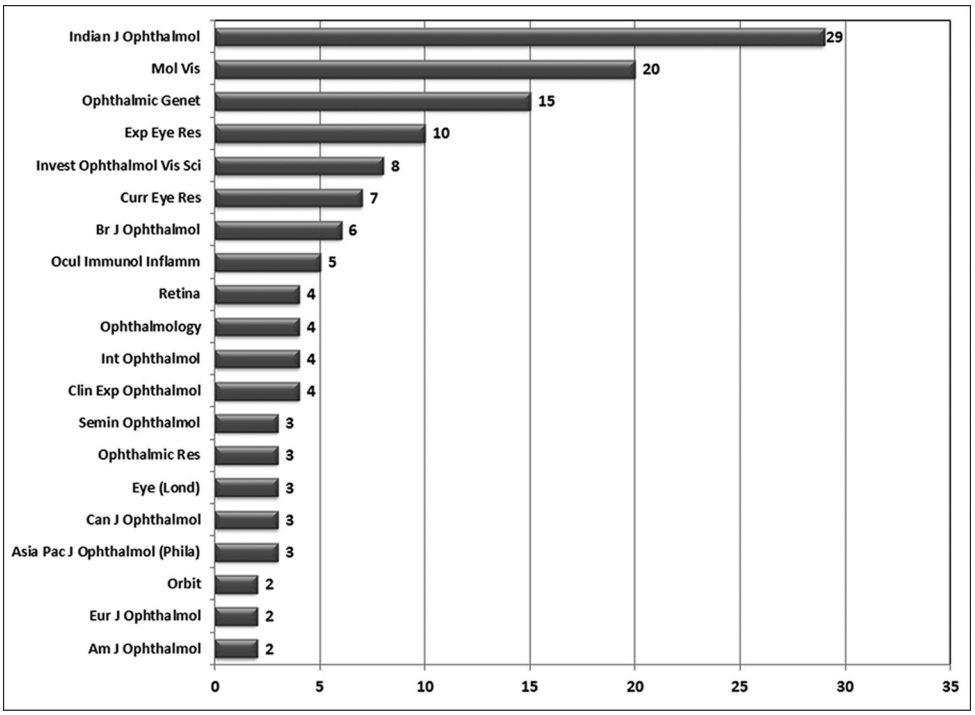

Figure 2: Numbers of articles published in different journals

number of publications. India accounted for only 3% of the publications (n = 341).

According to Mohan *et al.*,[3] the burden of genetic disorders in India is significant. In 1989, Kumaramanikavel collaborated with SN to start research in ophthalmic genetics that lead to a major achievement in this field in India.[11] The journey to map both syndromic and non-syndromic autosomal recessive genes involved in RP started in the mid-1990s in India.[11] The current study reflects the maximum number of publications (30%) from SN, which supports the trend in the significant contribution of this institute to the research on GRD.[12,13]

According to Thomas *et al.*,[14] most ophthalmology institutes do not have a research specialty, which is a major factor for the decreased number of publications. The other factors contributing to a low output of publications included lack of research training, inadequate access to basic science facilities, inability to collaborate as full partners with non-medical scientists, lack of financial resources, and inadequate medical record standards.[15]According to the current study, the leading eye institutes in terms of research output in the field of GRD were supported by their research departments. Interestingly four of the top six institutes are located in the southern part of India (SN at Chennai, L.V. Prasad Eye Institute at Hyderabad, Aravind Eye Hospital at Madurai, and Narayana Nethralaya at Bangalore) and the rest two (Post Graduate Institute of Medical Education and Research, Chandigarh, and Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi) in the northern part of India. Needless to say, India is having social, geographic, cultural, and economic diversity, and probably so does the GRD. These institutes, sharing their resources and infrastructure, may undertake projects in ocular genetics mentoring and collaborating with both existing and developing eye research institutes from the other parts of the country to bridge the gap in the field of research in ophthalmology of the region.

As per the WHO, genetic eye disorders are one of the top 10 major causes of global ocular health burden. Retinoblastoma

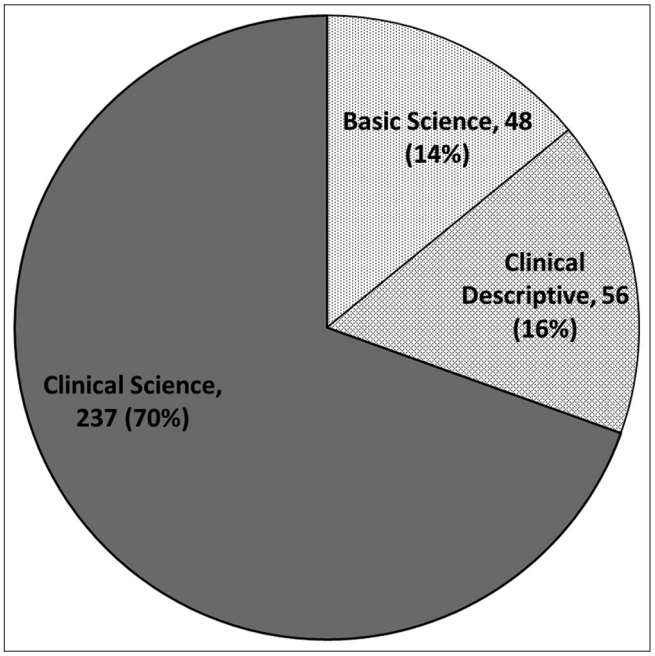

Figure 3: Classification of publications into different sub-types

is the most common childhood ocular malignancy and is having a significant genetic etiology. Retinoblastoma is the first malignancy of the eye, where the inheritance of the disease is directly demonstrated.[16] India carries the biggest burden of retinoblastoma globally, with an estimated 1,500 new cases annually. Recent advances in the genetics of retinoblastoma have helped in improving the overall clinical management of this malignancy.[17] Similarly, genetic factors play an important role in the pathogenesis of DR, the burden of which is on a rise in the working-age population.[18]The current study found the maximum number of research articles on retinoblastoma (24%)

Table 1: Research output of an individual institution

Institution	Number of Publication	%
Sankara Nethralaya	102	29.91
L V Prasad Eye Institute	28	8.21
Post Graduate Institute of Medical Education and Research	28	8.21
Aravind Eye Hospital	27	7.92
Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS	26	7.62
Narayana Nethralaya	13	3.81
Top six eye care centers combined	*n*=224	65%

Table 2: Author-wise contribution (top 10)

Name of authors	Number of publications
Raman R	28
Krishnakumar S	27
Khetan V	24
Sharma T	21
Biswas J	16
Gupta A	16
Anand A	14
Ganesan S	13
Kulothungan V	13
Sundaresan P	12
Top ten authors combined	*n*=184

Table 3: Publications in collaboration with other countries

Country	No. of publications
USA	36
UK	30
China	20
Australia	12
Singapore	8
Germany	7
Japan	6
Total	119

Table 4: Disease-wise publications

Diseases	Number of publications	%
Retinoblastoma	82	24.0
Diabetic retinopathy	78	22.9
Age-related macular degeneration	53	15.5
Retinitis pigmentosa	50	14.7
Leber congenital amaurosis	10	2.9
Juvenile X-linked retinoschisis	7	2.1
Norrie disease	3	0.9
Stargardt disease	3	0.9

and DR (23%). This finding echoes the focus on global research on important GRD in India, albeit in a small number.

In the current study, the journal-wise analysis revealed a greater number of articles were published in IJO. This may be because IJO is the only ophthalmic journal with an impact factor published in India.[19] The number of ophthalmology journals having an impact factor published in India should be increased and researchers from India should be encouraged to submit their research work for publication in these journals. International collaborative research supports many scientists and clinicians from India and this is on a rise.[20] This is reflected by a significant number (n = 119, 35%) of publications on GRD by Indian authors in collaboration with authors from outside India.

Gene therapy holds great hope for the treatment of a wide range of GRD. X-linked RP is the GRD with the maximum number of ongoing research on gene therapy, all of which rely on an adeno-associated virus (AAV)-mediated gene replacement therapy.[21]The Food and Drug Administration (FDA) approval of voretigene neparvovec (Luxturna) for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy has motivated the scientists and clinicians to further the research in gene therapy for the GRD.[22] The real-world evidence of safety and efficacy of voretigene neparvovec (Luxturna) demonstrate favorable outcomes in pediatric patients with RPE65-associated Leber congenital amaurosis.[22] A broader spectrum of therapies including delivery of genes encoding neurotrophic or neuroprotective factors, such as proinsulin or stanniocalcin-1 for combating the long-term photoreceptor loss, are being explored.[23] Similarly, gene therapy inhibiting complement systems has been studied for geographic atrophy in non-neovascular AMD.[23] Apart from gene therapy, genetic counseling, and low vision rehabilitation methods are helpful to improve the residual vision of patients with devastating GRD.[23] The genetic laboratories in India started in 2000 and are on a surge due to the generous support from different Government agencies such as the Department of Biotechnology (DBT), the Department of Science and Technology (DST), and the Indian Council of Medical Research (ICMR).[24] However, the laboratories conducting dedicated research in the field of GRD are limited in India and there is an urgent need for increasing their number. Collaboration between the DBT, India, and the National Eye Institute, USA is an important step in the progress of research in gene therapy for GRD in India.[25]Long-term follow-up of treated patients and advances in the field of genetic testing and molecular diagnostics are among the lines of research on gene therapy in India.[26] In the current study, only three articles by Indian authors were related to gene therapy. This shows the long way forward in the research on gene therapy in India.

Limitations

First, our analysis was based only on Medline. Reviewing other databases might give a better understanding of contributions from India. Second, some of the research related to GRD might have been started in the period defined in the current study but might not be published due to the ongoing phase of the study.

Conclusion

This bibliometric study of publications in the field of research on GRD in India shows that research productivity, as measured in both the number of publications in peer-reviewed journals and qualitative measures of those journals, has increased during the period of this study. However, the number of research articles in the field of GRD in comparison to developed countries such as the USA is minimal. The results of this study are an indicator of the productivity of Indian ophthalmologists and vision researchers. This analysis may be helpful to find out the obstacles of research productivity, which would help

to develop research capacity leading to an increased number of publications in the field of GRD.

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Conflicts of interest

There are no conflicts of interest.

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