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ORIGINAL RESEARCH

Trends in Congenital Insensitivity to Pain with Anhidrosis: A Bibliometric Analysis from 2000 to 2021

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Background: Congenital insensitivity to pain with anhidrosis (CIPA) is a very rare inherited autosomal recessive disease that has multiple clinical manifestations. Since its symptoms are related to different systems, this disorder has been investigated on a variety of topics. To better understand publications about CIPA, we conducted a bibliometric study to evaluate research publications on CIPA from 2000 to 2021, and delineate the key contributions in terms of countries, authors and sources.

Methods: Quantitative analysis of publications on CIPA from 2000 to 2021 was interpreted and graphed through the Science Citation Index Expanded (SCIE) of Web of Science (WOS) Core Collection. The bibliometric package in R 4.1.1, VOSviewer 1.6.18, and GraphPad Prism 8.4 were used to conduct the bibliometric analysis.

Results: From 2000 to 2021, a total of 163 publications were retrieved. China had the largest number of publications (n = 31), while Japan had the highest number of citations (621 citations). Levy J and Indo Y were perhaps the most impactful researchers in the field of CIPA. The co-authorship of authors and institutions indicated little cooperation on CIPA research between different countries. *Annals of Neurology* (n=5) and *Nature Genetics* (120 citations) were the most productive and cited journals, respectively, and the top 10 local cited references clarified the theoretical basis of the CIPA research area. Furthermore, the important topics on CIPA mainly include *NTRK1* mutations and nerve growth factor (NGF).

Conclusion: Based on the bibliometric analysis, we have a comprehensive view of the global status of CIPA research, and the results indicate that CIPA needs more attention and cooperation to facilitate the study of its pathological mechanisms.

Keywords: congenital insensitivity to pain with anhidrosis, bibliometric analysis, VOSviewer

Introduction

Congenital insensitivity to pain with anhidrosis (CIPA) is a very rare inherited autosomal recessive disease, which is also known as hereditary sensory and autonomic neuropathy type IV.[1] The main clinical manifestations of CIPA include insensitivity to painful stimuli, absence of sweating, self-mutilating behaviors, variable mental retardation, and varying degrees of trauma resulting from bone and joint fractures.[2] It is generally believed that the pathogenesis of CIPA is caused by mutations in the neurotrophin receptor kinase 1 (NTRK1) gene.[3] However, some researchers found that not all *NTRK1* mutations could result in downstream signaling pathway dysfunction, suggesting that *NTRK1* mutations may not be the only pathogenesis of CIPA.[4] Since the first CIPA case was reported in 1963,[1] sporadic cases were reported around the world subsequently, such as Japan,[5] Israel,[6] and China.[7] Previous studies focused on reporting new cases of CIPA and finding new mutation sites of *NTRK1*. In recent years, with the rapid development of some research fields, studies have begun to study CIPA from the perspective of microbiology and metabolomics.[8–10] Despite different significant researches on CIPA have been conducted, various CIPA-related scientific issues still require additional and continued exploration and scholarly contributions. Thus, it is essential to evaluate the research performance in relevant areas to better prepare for further study.

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Bibliometric analysis can assess influential publications in a certain study area and objectively evaluate their study impact. At present, there is no scientific report on the bibliometric analysis of CIPA. The purpose of this study was to evaluate research publications on CIPA from 2000 to 2021 to delineate the key contributions in terms of countries, authors, and sources. Besides, the research hotspots of CIPA were investigated to help understand its current research status and provide scientists with new ideas for studying CIPA.

Methods

Data Source

In this study, all data were retrieved from the Science Citation Index Expanded (SCIE) of Web of Science (WOS) Core Collection on April 26, 2022. The search term was "Congenital insensitivity to pain with anhidrosis" (All Fields) with a publication timespan from 2000 to 2021. All final records were downloaded in txt format on April 26, 2022, and imported into visualization and bibliometrics tools for further analysis.

Statistical Analysis

The bibliographic records of the retrieved publications were converted and analyzed automatically using the bibliometric package in R 4.1.1, including the distribution of countries/regions, years of publication, journals, and authors. VOSviewer 1.6.18 was used to visualize the co-authorship analysis of authors and institutions, and co-occurrence analysis of keywords.[11] The journal impact factors used for individual publications were collected from the 2020 Journal Citation Reports (JCR). Data on the annual output of publications, productive countries, and top authors were analyzed by GraphPad Prism 8.4.

Results

Year and Country of Publication

From 2000 to 2021, the total number of publications about CIPA was 163, and among these, 124 were categorized as "article", and 8 were categorized as "review" (Table 1). The annual number of papers fluctuated slightly, and the year with the largest number of papers published was 2013 (n = 14) (Figure 1A). Furthermore, we also analyzed the contributions provided by different countries based on the number of papers. The top 20 productive countries are shown in Figure 1B. China contributed the largest number of papers (n = 31), followed by Japan (n = 25), Israel (n = 18), Italy (n = 12), and the United States (n = 12) (Figure 1B). Moreover, studies from Japan had the highest number of citations (621 citations), followed by Italy (468 citations), Israel (302 citations), China (156 citations), and the United States (156 citations) (Figure 1C). A total of 9 countries with more than five publications in the field were analyzed in the co-authorship analysis (Figure 1D). The five countries with the highest total link strength were the United States (total link strength = 12 times), Israel (5), Japan (5), Italy (4), and China (4).

Analysis of Authors

From 2000 to 2021, Levy J was the most productive author with 15 papers on CIPA, followed by Indo Y (13 papers), Pinsk V (8 papers), Liu Y (6 papers), and Mardy S (6 papers) (Figure 2A). Moreover, the contributions of the author were evaluated by the counts of total citations. Local citation is a measure for evaluating the influence of scientists and their papers in the CIPA research area.[12,13] In terms of local citations, Endo F was ranked first (81 citations), followed by

Table 1 Summary of Document Types

Document Types	Number
Article	124
Editorial material	9
Letter	15
Meeting abstract	7
Review	8

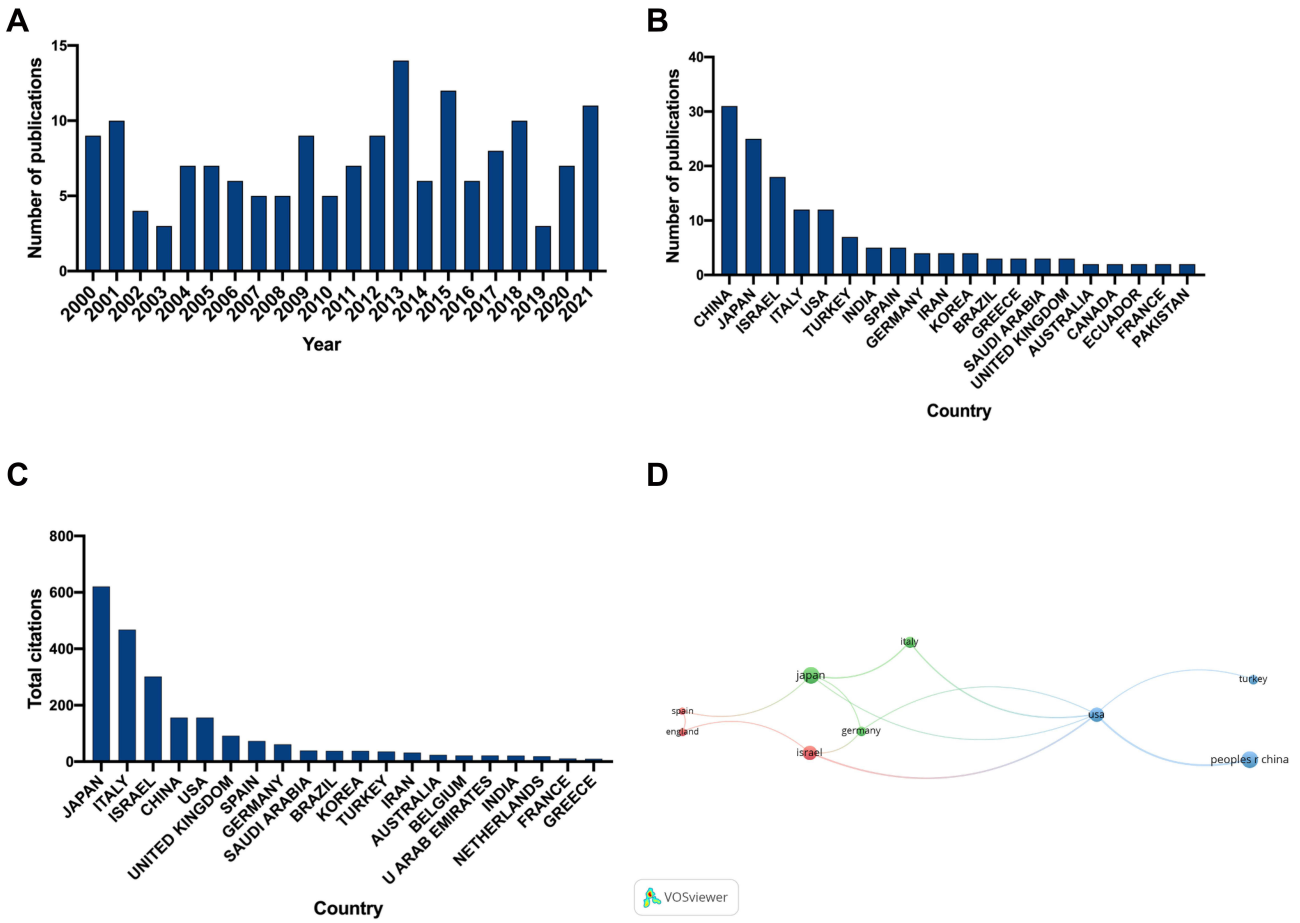

Figure 1 Global trends in publications on CIPA research and contributions of countries. (**A**) Annual publication output from 2000 to 2021. (**B**) Top 20 countries with the largest number of publications. (**C**) Total citations of related papers from different countries. (**D**) Network map of countries/regions related to CIPA research with more than five publications.

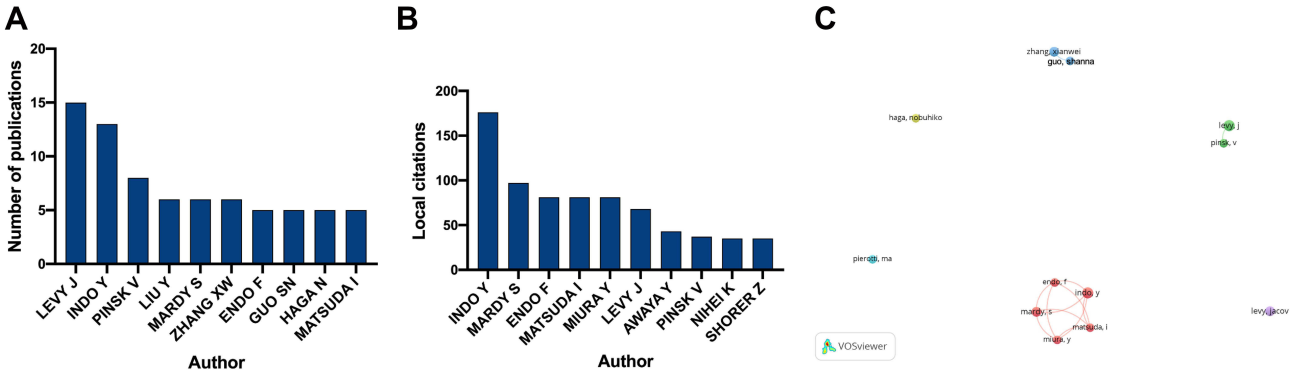

Figure 2 Author contributions. (**A**) Number of publications from different authors. (**B**) Local citations in the research field from different authors. (**C**) Network visualization map of co-authorship between authors with more than five publications.

Matsuda I (81 citations), Miura Y (81 citations), Levy J (68 citations), and Awaya Y (43 citations) (Figure 2B). The network map also showed collaboration from the authors (Figure 2C).

Analysis of Institutions

The top 10 institutions with papers published on CIPA, as shown in Figure 3. The most active institution was the *Ben-Gurion University of the Negev* in Israel (n=31), followed by *Huazhong University of Science and Technology* in China

Figure 3 Institution distributions. The top 10 most productive institutions for CIPA research. (**B**) Network visualization map of co-authorship between institutions with more than five publications. (**C**) Overlap visualization map of co-authorship between institutions with more than five publications.

(n=9), *Chonnam National University* in South Korea (n=8), *Kumamoto University* in Japan (n=8) and the *University of Tokyo* in Japan (n=8), (Figure 3A). In Figure 3B, the network map also showed collaboration from the institutions, which occurred more than five times from 2000 to 2021. The colors in the overlap visualization indicated the average publication year of the identified institutions (Figure 3C).

Analysis of Journal

We analyzed the top 10 journals with papers published on CIPA, as shown in Table 2. As a result, the journals with the largest number of papers were *Annals of Neurology, Neuromuscular Disorders* and *Pediatric Anesthesia* (n = 5), followed by *Human Mutation*, and *Pediatric Neurology* (n = 4). In addition, the top 10 cited journals were also evaluated. *Nature Genetics* had the largest number of citations (120 citations), followed by *Archives of Neurology* (102 citations), *Pediatric Neurology* (101 citations), *Nature* (95 citations), and *American Journal of Human Genetics* (92 citations) (Table 2).

Citations

Table 3 lists the top 10 references with the highest local citations. The top three local cited references were "Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis" (96 citations);[14] "Congenital

Table 2 Top 10 Popular Journals and Cited Journals

Rank	Popular Journals	Records (n)	2020 Impact Factor	2020 JCR Partition	Cited Journals	Citations (n)	2020 Impact Factor	2020 JCR Partition
1	Annals of Neurology	5	10.422	Q1	Nature Genetics	120	38.33	Q1
2	Neuromuscular Disorders	5	4.29	Q2	Archives of Neurology	102	/	/
3	Pediatric Anesthesia	5	2.55	Q2	Pediatric Neurology	101	3.372	Q2
4	Human Mutation	4	4.87	Q1	Nature	95	49.96	Q1
5	Pediatric Neurology	4	3.37	Q1	American Journal of Human Genetics	92	11.02	Q1
6	American Journal of Medical Genetics	3	2.80	Q3	Human Mutation	90	4.87	Q1
7	British Journal of Dermatology	3	9.30	Q1	Journal of Biological Chemistry	86	5.15	Q2
8	Human Genetics	3	4.13	Q2	Oncogene	72	9.87	Q1
9	Journal of Child Neurology	3	1.987	Q4	Cell	63	41.58	Q1
10	Journal of Pediatric Orthopaedics-Part B	3	1.04	Q4	Journal of Neuroscience	59	6.17	Q1

Table 3 Top 10 Local Citation Analysis of References on CIPA Research

Rank	Title	First Author	Source	Country	Citations (n)
1	Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis	Yasuhiro Indo	*Nature Genetics*	England	96
2	Congenital insensitivity to pain with anhidrosis. A unique syndrome in two male siblings	A.G. Swanson	*Archives of Neurology*	United States	59
3	Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV)	Rosemberg S	*Pediatric Neurology*	United States	56
4	Congenital insensitivity to pain with anhidrosis: novel mutations in the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor	S Mardy	*American Journal of Human Genetics*	United States	51
5	Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies	S Shatzky	*American Journal of Medical Genetics*	United States	41
6	Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families	Y Miura	*Human Genetics*	United States	35
7	Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor	Yasuhiro Indo	*Human Mutation*	United States	33
8	Eccrine sweat glands are not innervated in hereditary sensory neuropathy type IV. An electron-microscopic study	J Langer	*Acta Neuropathologica*	Germany	33
9	Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene	R J Smeyne	*Nature*	England	26
10	Anatomic changes in congenital insensitivity to pain. Absence of small primary sensory neurons in ganglia, roots, and Lissauer's tract	A.G. Swanson	*Archives of neurology*	United States	25

insensitivity to pain with anhidrosis. A unique syndrome in two male siblings" (59 citations);[1] and "Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV)" (56 citations).[15]

Co-Occurrence Analysis of Keywords

The frequency of two keywords that appeared together in the same publication indicated research hotspots. The size of the circles and the thickness of the line represented the frequency of co-occurrence of the keywords. In Figure 4A, we analyzed a total of 48 keywords that were identified as having occurred more than five times. The colors in the overlap visualization indicated the average publication year of the identified keywords (Figure 4B), and the results showed that the majority of the keywords were published after 2012, with greener or yellower colors. In addition, the density visualization showed the same identified keywords mapped by frequency of appearance, and keywords in yellow occurred with the highest frequency (Figure 4C).

Discussion

In this study, we combined bibliometric analysis with network visualizations to delineate the current landscape of the research on CIPA from 2000 to 2021. The results showed that the annual publication output about CIPA fluctuated slightly, and the number of papers published per year was less than 20, indicating that rare diseases received low attention. China was ranked first in the total number of publications, this may be related to the larger population in China leading to more cases. Zhang et al reported heterogeneity of clinical features and mutation analysis of *NTRK1* in Han Chinese patients with CIPA, and a total of 41 patients were included in the analysis. Furthermore, their study suggested that c.851–33T>A may be a common pathogenic site in Han Chinese patients.[2] To our knowledge, that was the most comprehensive and extensive report of CIPA around the world. In addition, the number of studies that were conducted in the top five countries accounted for 50% of all included studies, indicating that most researches on CIPA were limited to

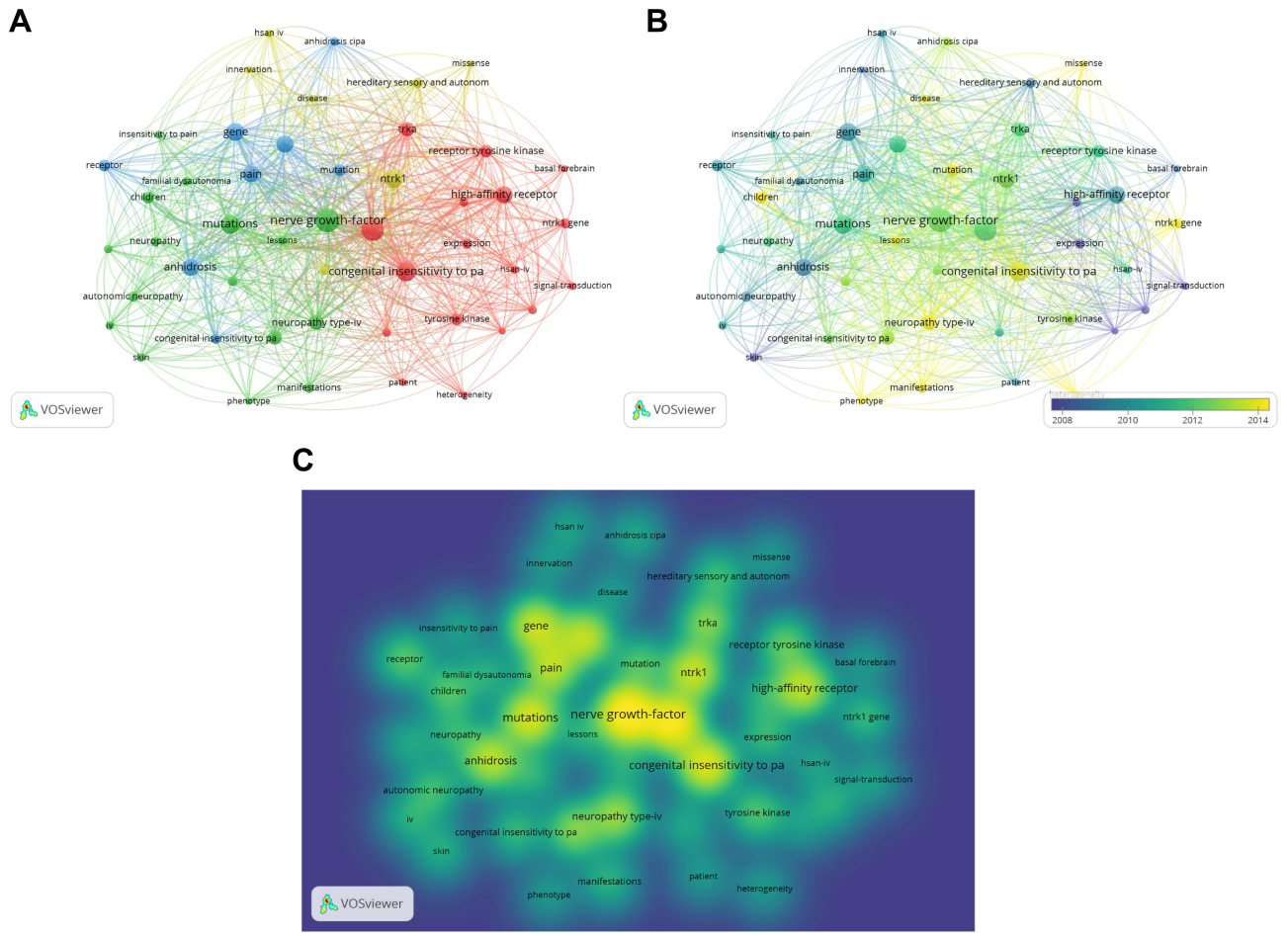

Figure 4 Co-occurrence analysis of keywords. (**A**) Network visualization map of keywords. (**B**) Overlap visualization map of keywords. (**C**) Density visualization map of keywords.

a small number of countries. Moreover, Japan was ranked first in the total citations of publications, suggesting that this country may have a more significant impact on the direction of research in a related field.

Levy J is the pioneered scientist who has reported the largest number of publications in the field of CIPA and most of his reported cases were in Israel.[16] Since mental retardation and susceptibility to infection are major complications of CIPA, the publications of Dr. Levy were mainly focused on these two characteristics of CIPA children in Israel.[16–19] Their team found that children with CIPA mainly have infections of the skin and skeleton and that the most frequent pathogen is *Staphylococcus aureus*.[16] In addition, they assessed cognitive and adaptive behavior among twenty-three Arab Bedouin children with CIPA and found that children with CIPA functioned in the mental retardation range.[18] Although Dr. Levy has not published papers on CIPA patients since 2014, he is also a prominent researcher in the research field and is responsible for the recognition that patients with CIPA have many different phenotypes. Indo Y and Pinsk V are the other two most influential authors of the top three. Indo Y is from Japan, while Pinsk V and Levy J come from the same institution. Since CIPA results from loss-of-function mutations in the *NTRK1* gene-encoding tropomyosin-related kinase A (TrkA), a receptor for nerve growth factor (NGF), Indo Y is interested in the correlation between CIPA and NGF, and mainly focused on the mechanism of NGF.[19,20]

Furthermore, most type of Indo Y's published papers is "review", through these reviews, Indo Y described the role of NGF-TrkA signaling pathway in pain, itch, emotion, and cognition, all of which were inspired by CIPA.[20–24] Meanwhile, since Pinsk V is a co-author of the publications of Levy J, the publications of Pinsk V are also focused on CIPA cases in Israel.[6,25] Interestingly, since the NGF-TrkA signaling pathway participated in the endocrine pancreas morphogenesis and insulin secretion in vitro, Pinsk et al found the first phase insulin response was impaired or borderline in CIPA patients.[25]

However, the sample size of the previous study was small, and more studies on the clinical significance of NGF-TrkA effects on insulin secretion are required. We also analyzed the co-authorship of authors around the world. However, in terms of co-authorship, we found no collaboration between authors from different countries. These results suggested a lack of international collaboration in studies on CIPA, and enhanced collaboration and case sharing would further promote the development of studies on CIPA.

Next, we analyzed the top ten institutions which contributed to CIPA research. The *Ben-Gurion University of the Negev* had the largest number of publications since Levy J was a researcher at this institution, he contributed a lot to the publications of this university. Notably, in the top ten authors, Zhang XW and Guo SN belonged to the same team, which was affiliated to *Huazhong University of Science and Technology*, contributed to the number of publications on CIPA in this institution. Similarly, we analyzed the situation of co-authorship between institutions, and the results also indicated a lack of international collaboration in studies on CIPA. Since these universities with the largest number of publications are strong comprehensive strength institutions in their own country, maybe enhanced cooperation through school platforms will facilitate CIPA research.

The top ten journals wherein papers on CIPA were mainly in the field of neurology and pediatrics, as shown in Table 2. This may be due to the fact that CIPA is a congenital neurodevelopmental disorder with a high incidence in children. Moreover, the impact factor (IF) of most CIPA publications is low, which may be due to the fact that most studies of CIPA focus on the discovery of new mutational sites and lack in-depth research. Therefore, innovative findings are needed to be published in journals with high IF. For example, Norcliffe-Kaufmann et al examined the effect of posture on heart rate, blood pressure, plasma concentration of catecholamines, vasopressin, endothelin, and renin activity in patients with CIPA. They found that plasma norepinephrine levels were very low or undetectable and failed to increase when the patient was upright, yet upright blood pressure was well maintained.[26] This study not only confirms the postganglionic sympathetic neurons are severely depleted in CIPA, but also may provide a new reference for blood testing in patients with CIPA.

The local citation analysis of references showed that Indo et al had the highest number of citations, which identified defects in TRKA cause CIPA and that the NGF-TRKA system had a crucial role in the development and function of the nociceptive reception as well as the establishment of thermoregulation via sweating in humans.[14] Meanwhile, the journal *Nature Genetics*, in which this paper was published, also had the highest number of citations. In addition, half of the top ten cited references were case reports, suggesting that the main research topics on CIPA were the discovery of new cases and the summary of phenotypes of CIPA patients.

Next, we also analyzed the co-occurrence network of keywords to indicate the current hot topics and future directions in CIPA research. Since the discovery of new mutational sites was a major focus of CIPA research, studies of mutations were always hot topics in this field. In addition, the function of NGF is becoming more and more interesting to researchers in the related area since the main pathological mechanism of CIPA is the disorder of the NTRK1/NGF signaling pathway. A few researchers learned a lesson from CIPA to study the role of NGF in pain or neurodevelopment, such as Indo Y,[21] and that was an important idea for further research on the pathogenesis of CIPA. The network indicated that case reports and mechanisms of main signaling pathways in CIPA will continue to be the research hotspot in this area.

To the best of our knowledge, this is the first bibliometric analysis focusing on CIPA, nevertheless, there were some limitations of this study. First, since the data were limited to the SCIE of Web of Science Core Collection database, only publications published in English were extracted, which resulted in inclusion bias. Second, newly published papers had few citations, this does not mean that these papers were not important. Therefore, it is necessary to observe the latest publications.

Conclusion

We analyzed 163 English publications on CIPA from 2000 to 2021. Despite some limitations, this study has comprehensively presented the current state of CIPA research. The results indicated that some researchers in Israel, Japan, and China were following a cohort of CIPA patients, but they did not collaborate. The *Annals of Neurology* and *Nature Genetics* ranked first in the productive journals and cited journals, respectively. Meanwhile, we used the top ten citations

of references to clarify the theoretical basis of the CIPA research area. Overall, rare diseases like CIPA need more attention and cooperation to facilitate the study of its pathological mechanisms.

Abbreviations

CIPA, Congenital insensitivity to pain with anhidrosis; NTRK1, Neurotrophin receptor kinase 1; SCIE, Science Citation Index Expanded; WOS, Web of Science; JCR, Journal Citation Reports; NGF, Nerve growth factor; TrkA, Tropomyosin-related kinase A.

Data Sharing Statement

The datasets supporting the conclusions of this article are included within the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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