

Knowledge Mapping of Cowden Syndrome: a Bibliometric Analysis

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Objective: To provide a comprehensive overview of the current knowledge structure and research hotspots of Cowden syndrome via bibliometrics.

Methods: The articles and reviews related to Cowden syndrome were included from the Web of Science Core Collection (WoSCC) database. VOSviewer, CiteSpace and GraphPad Prism were used to conduct the bibliometric analysis.

Results: The number of papers focusing on Cowden syndrome was relatively low initially but increased rapidly from 1997 to 1999, and then maintained small-scale fluctuation. A total of 1,557 papers from 65 countries/regions and 1,762 institutions were identified. The USA was the most productive country, and Ohio State University was the most productive institution. In terms of the number of publications, Human Molecular Genetics ranked first, and Cancer Research was the most frequently cited journal. Eng was the most productive author, and Liaw was the most co-cited author. Phosphatase and tensin homologue (PTEN), germline mutations, gene, cancer, mutations, tumour suppressor gene and breast were high-frequency key words in this field.

Conclusion: This study was the first comprehensive bibliometric overview of the current state and development of Cowden disease. The mutation of PTEN and associated cancers, especially breast, thyroid and endometrial cancer, could be the focus of future research in this field.

Keywords: bibliometric analysis, Cowden syndrome, germline mutation, PTEN
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Cowden syndrome is a rare inherited condition in an autosomal dominant pattern, characterised by multiple hamartomas in different organs. It is also known as Cowden disease and multiple hamartoma syndrome, and is a rare multisystemic cancer predisposition disorder, with the breast, thyroid, endometrium and kidney being the most frequently involved organs.¹ Mucocutaneous lesions and macrocephaly are common clinical manifestations in patients with Cowden syndrome.²

Pathognomonic mucocutaneous lesions with verrucous manifestations are believed to exist in 100% of patients with Cowden syndrome by the age of 30. The verruca has different descriptions including “tricholemmomas”, “inverted follicular keratosis”, “oral papillomas” and “acral and palmoplantar keratosis” based on morphological appearances.^{1,3} Cowden syndrome is inherited in an autosomal dominant pattern with mutations in the tumour suppressor gene phosphatase and tensin homologue (PTEN), which is categorised as a member of the spectrum of PTEN hamartoma tumour syndrome (PHTS).⁴ The incidence of Cowden syndrome is reported to be approximately 1/200,000 individuals worldwide.^{5,6}

Bibliometrics is a method of literature analysis that evaluates the output and status in a specific research field quantitatively and qualitatively, providing visual representations of the current research and playing an important role in the prediction of future developments.^{7,8} Information about the publishing countries/regions, institutions, journals and co-cited journals, authors and co-authorship, citations, references, key-

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words and the frontiers of research activities can be visualised by knowledge mapping.^{9,10} CiteSpace and VOSviewer are commonly used software in data processing and analysis.

The application of bibliometric analysis is used widely in other fields nowadays, but to the best of the present authors' knowledge, so far, there is no relevant bibliometric analysis in the field of Cowden syndrome. Cowden syndrome, a rare disease with phenotypic variability, can easily lead to missed diagnosis and misdiagnosis. Its onset greatly affects patients' quality of life, and timely and accurate diagnosis and treatment are crucial to alleviate their pain. Thus, it is necessary to summarise and analyse the current research to help clinical physicians achieve a more comprehensive understanding of the disease. In this study, the present authors searched the Web of Science Core Collection (WoSCC) database to gather publications about Cowden syndrome from 1972 to 2023 and performed a bibliometric analysis to describe the current research progress and explore the hotspots and developmental trends in the field for future research.

Materials and methods

Sources of data and search strategies

The relevant publications related to Cowden syndrome were searched from the WoSCC database with the science citation index expanded (SCI-expanded). The search formula was (((TS = (Cowden syndrome)) OR TS = (Cowden disease)) OR TS = (multiple hamartoma syndrome)) OR TS = (face deformity-oral papillomosis syndrome). The type of publication was set to "articles" and "reviews", and the language of publication selected was English. All the data were downloaded within one day on 6 May 2023 and saved as a plain text file for further analysis.

Data collection and analysis

Under these conditions, a total of 1,557 records were identified, composed of 1,258 articles and 299 reviews. Among the 1,258 articles, the top 10 medical fields in which these were found were Oncology (278), Genetics Heredity (254), Dermatology (148), Pathology (122), Biochemistry Molecular Biology (119), Clinical Neurology (101), Surgery (97), Endocrinology Metabolism (70), Cell Biology (66) and Gastroenterology Hepatology (64). The bibliometric analyses were performed using CiteSpace (version 6.2.R3), VOSviewer (version 1.6.11) and GraphPad Prism (version 9) to visualise the data.

Results

Quantitative analysis of publications

There was an overall upward trend in the number of publications released each year on Cowden syndrome from 1972 to 1999, then this continued to fluctuate within a narrow range from 2000 to 2023 (Fig 1). Specifically, the number of publications remained relatively low from 1972 to 1990, with a mean of 1.73 a year. From 1991 to 1996, a slow-growth rate was observed in the number of publications, with a mean of 10.33 a year. From 1997 to 1999, the number of relevant publications increased rapidly, with a mean of 57.33 a year. From 1999 to 2022, the number continued to fluctuate within a narrow range, with a mean of 56 a year.

Countries/regions and institutions

A total of 65 countries/regions and 1,762 institutions were found to have contributed greatly to this field. We obtained a national collaboration diagram and observed close cooperation among the countries when the minimum number of documents published per country was set at 5 (Fig 2a). The top 10 countries/regions were the USA (831 publications, 53.37% of all articles), England (156, 10.02%), Japan (121, 7.77%), Italy (83, 5.33%), France (82, 5.27%), Canada (81, 5.20%), Germany (80, 5.13%), People's Republic of China (68, 4.37%), the Netherlands (48, 3.08%) and Spain (47, 2.77%) (Table 1 and Fig 2b).

The present authors set a minimum publication threshold of 10 documents per institution, which revealed the top 42 institutions and their collaborative relationship (Fig 2c). The size of the circles is proportional to the number of publications, and the lines between two circles indicate collaboration. Strong collaboration was found between Cleveland Clinic and Case Western Reserve University, and between Harvard University and the University of Cambridge. The top 10 institutions with the most publications are shown in Table 1 and Fig 2d. Ohio State University (108 publications, 6.94% of all articles) contributed the most publications, followed by Case Western Reserve University (103, 6.62%), Cleveland Clinic (100, 6.42%), Harvard University (74, 4.75%), the University of Cambridge (65, 4.17%), the National Cancer Institute (33, 2.12%), the University of Toronto (31, 1.99%), Dana-Farber Cancer Institute (26, 1.67%), Massachusetts General Hospital (26, 1.67%) and Mayo Clinic (26, 1.67%). Most of the top 10 institutions were based in the USA, except for the University of Cambridge (England) and the University of Toronto (Canada).

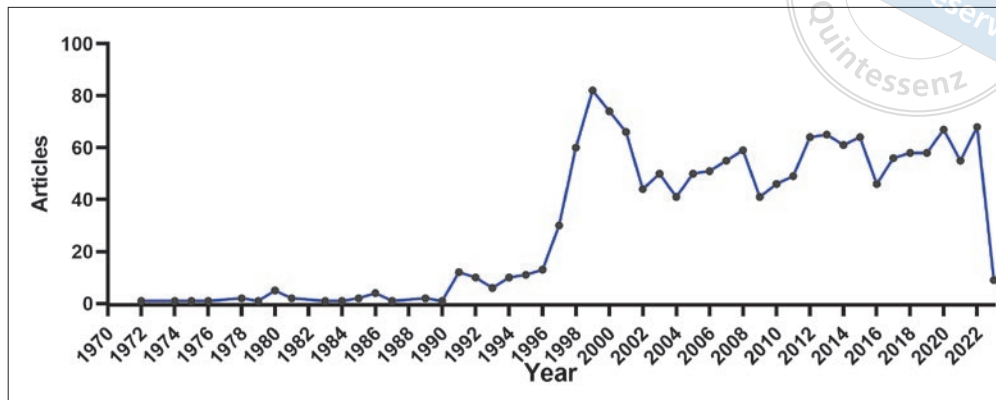


Fig 1 Annual output and global trends in publications on Cowden syndrome from 1972 to 2023.

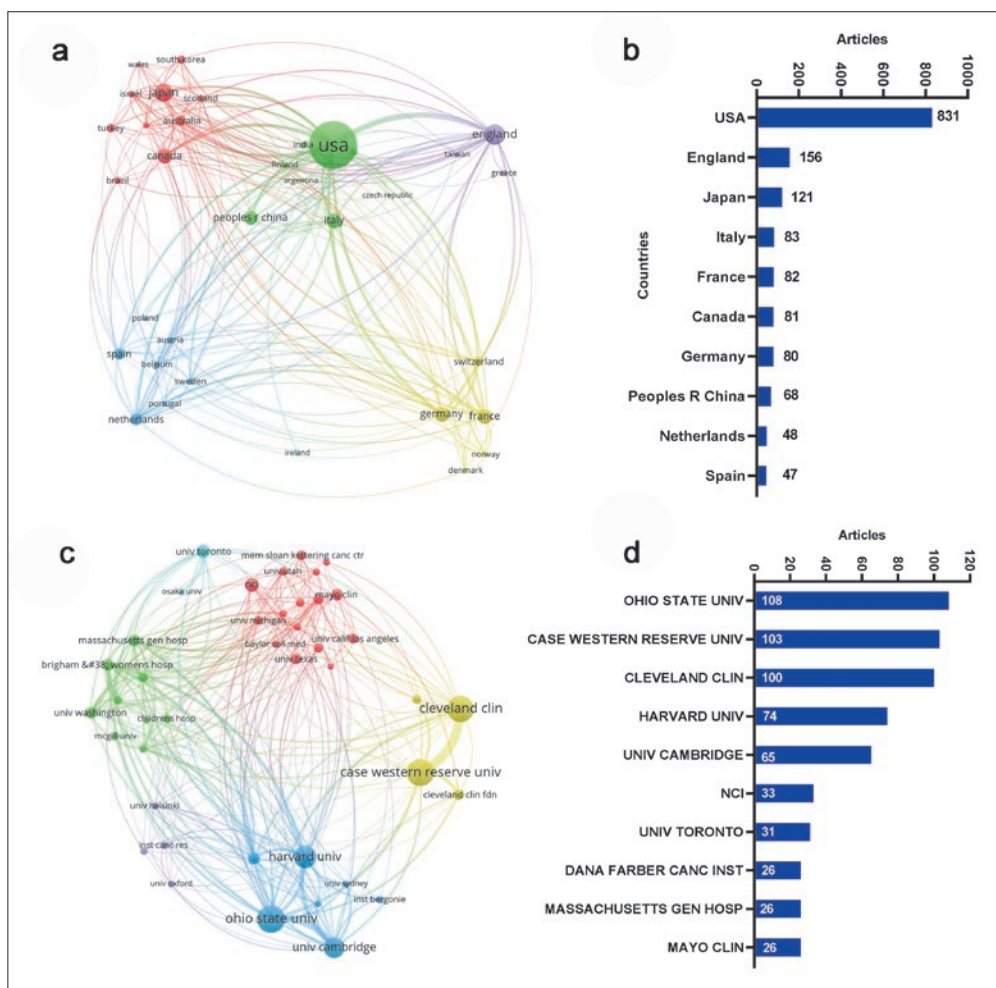


Fig 2 Distribution of countries/regions and institutions having published articles on Cowden syndrome. Network map of countries/regions with more than five publications (a). Top 10 countries/regions with total articles (b). Network map of institutions with more than 10 publications (c). Top 10 institutions with total articles (d).

Authors and co-cited authors

A total of 7,415 authors were identified in the 1,557 papers. A strong collaborative network was found among these authors, contributing to this research area (Fig 3a). Eng showed strong cooperation with other researchers (Fig 3a) and was also the most productive author (190

articles), followed by Meter (27) and Zhou (20) (Fig 3b). The co-cited author is an author cited by more than two researchers simultaneously. The co-citation network is depicted in Fig 3c. The minimum number of citations was set at 100, and 44 of the total 26,322 co-cited authors met this threshold, with Liaw (204 times) ranking first, followed by Marsh (187) (Fig 3d).

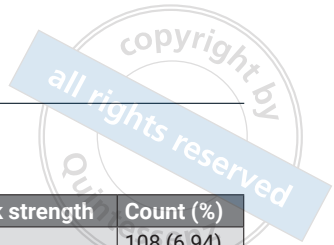


Table 1 The top 10 countries/regions and institution in publication.

Rank	Country	Total link strength	Count (%)	Institution	Total link strength	Count (%)
1	USA	377	831 (53.37)	Ohio State University (USA)	154	108 (6.94)
2	England	229	156 (10.02)	Case Western Reserve University (USA)	138	103 (6.62)
3	Japan	70	121 (7.77)	Cleveland Clinic (USA)	140	100 (6.42)
4	Italy	48	83 (5.33)	Harvard University (USA)	119	74 (4.75)
5	France	92	82 (5.27)	University of Cambridge (England)	139	65 (4.17)
6	Canada	72	81 (5.20)	National Cancer Institute (USA)	25	33 (2.12)
7	Germany	104	80 (5.13)	University of Toronto (Canada)	43	31 (1.99)
8	China	29	68 (4.37)	Dana-Farber Cancer Institute (USA)	90	26 (1.67)
9	Netherlands	81	48 (3.08)	Massachusetts General Hospital (USA)	67	26 (1.67)
10	Spain	31	47 (2.77)	Mayo Clinic (USA)	16	26 (1.67)

Journals and co-cited journals

The 1,557 publications were found to have been published in 596 journals. With the minimum number of documents per journal set at 10, 28 journals met the threshold (Fig 4a). Among the top 10 journals, the Journal of the American Academy of Dermatology showed the highest impact factor (IF) of 15.487, followed by Cancer Research (IF₂₀₂₁ = 13.312) and Proceedings of the National Academy of Sciences of the United States of America (IF₂₀₂₁ = 12.779) (Table 2).

The present authors also identified 4,642 co-cited journals. When the minimum number of articles per journal was set at 200, 64 journals met the threshold (Fig 4b). The circle size is directly proportional to the number of documents, and the three colours represent three different clusters. The higher the frequency of co-citation, the greater the impact of the journal. Cancer Research was cited most frequently (3,456 citations), followed by Nature Genetics (2,920) and Journal of Medical Genetics (2,059) (Fig 4b and Table 2). Among the top 10 journals, the journal with the highest IF was Cell (IF₂₀₂₁ = 66.85), followed by Science (IF₂₀₂₁ = 68.832) and Nature Genetics (IF₂₀₂₁ = 41.376). The majority of the top 10 journals and all the top 10 co-cited journals were distributed in Q1 according to the journal citation reports in 2022 (Table 2).

The dual map overlay of journals displayed the distribution of relationships between journals and cited journals, which were shown on the left and right, respectively. This citation path displayed the linkage of the different research fields. There were two main paths. The orange path suggested that papers published in molecular/biology/immunology journals commonly cited papers in molecular/biology/genetics journals, and the green path suggested that papers published in medicine/medical/clinical journals commonly cited papers in molecular/biology/genetics journals and in health/nursing/medicine journals (Fig 4c). The top 25

cited journals with the strongest citation bursts are presented in Fig 4d, among which Genetics in Medicine (strength 38.6) showed outbreak citations most recently from 2012 to 2023, followed by PLOS One (strength 33.88) and Nature Reviews Molecular Cell Biology (strength 19.02).

Keywords

Keywords are, to some degree, the reflection of research hotspots. Thus, they help scholars to understand the research frontiers in specific fields. In this study, there were 4,927 keywords overall, 51 of which were used in more than 40 publications. In Fig 5a, the size of circles positively correlated with keyword frequency and the thickness of the line of the circle positively correlated with the strength of relationships between keywords. Germline pten, individuals and pten hamartoma tumour syndrome were newly emerging keywords. Cowden syndrome, cowden disease, pten, germline mutations, gene, cancer, mutations, diseases, tumour-suppressor gene and breast were top 10 keywords with a high frequency from 146 to 484 (Fig 5b).

A category cluster analysis was performed to generalise the keywords in the co-citation network to understand the frontier directions. These keywords were divided into nine clusters, including oncology (#0), biochemistry and molecular biology (#1), genetics and heredity (#2), clinical neurology (#3), obstetrics and gynaecology (#4), public, environmental and occupational health (#5), radiology, nuclear medicine and medical imaging (#6), surgery (#7) and paediatrics (#8) (Fig 5c). The top 20 keywords with the strongest citation burst are shown in Fig 5d. The most intense keyword was cowden syndrome (27.77), followed by cowden-disease (24.06) and hamartoma tumour syndrome (17.05). The keyword with the longest burst time was cowden syndrome, which lasted 11 years from 2012 to 2023. More meaningfully, the keywords cowden syndrome,

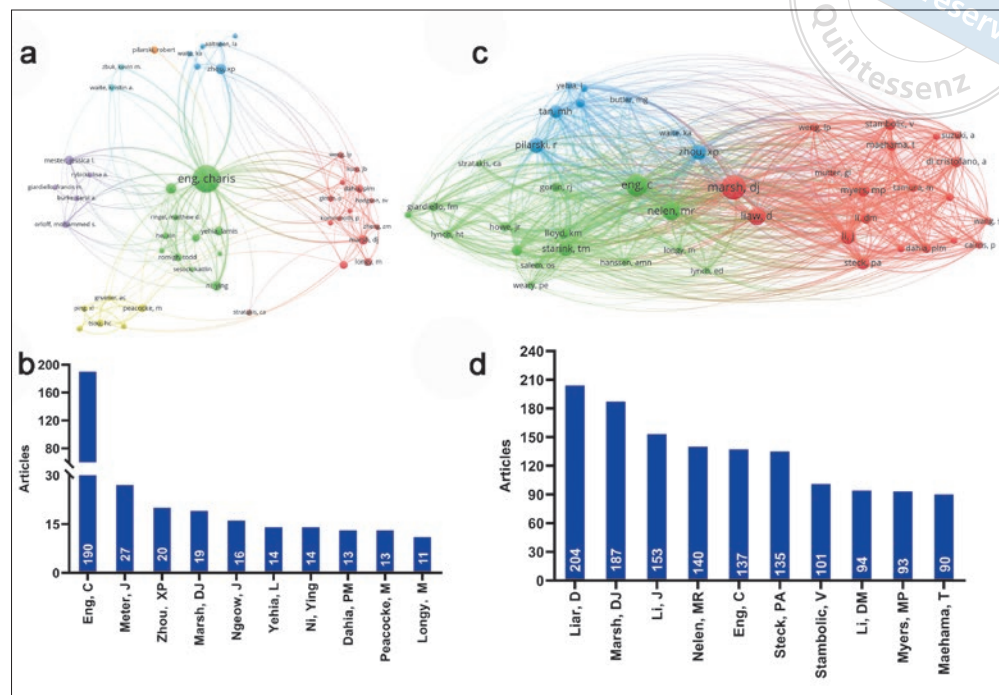


Fig 3 Analysis of authors and co-cited authors on Cowden syndrome. Network map of co-authorship between authors with more than five articles (a). Top 10 authors with total articles (b). Network map of co-authorship between co-cited authors with more than 100 articles (c). Top 10 co-cited authors with total articles (d).

Table 2 The top 10 most productive journals and co-cited journals.

Rank	Journal	Number of articles	IF (2021)	JCR (2021)	Co-cited journal	Number of citations	IF (2021)	JCR (2021)
1	Human Molecular Genetics	36	5.121	Q1	Cancer Research	3,456	13.312	Q1
2	Cancer Research	34	13.312	Q1	Nature Genetics	2,920	41.376	Q1
3	Oncogene	31	8.756	Q1	Journal of Medical Genetics	2,059	5.945	Q1
4	Journal of Medical Genetics	30	5.945	Q1	American Journal of Human Genetics	1,921	11.043	Q1
5	American Journal of Human Genetics	23	11.043	Q1	Proceedings of the National Academy of Sciences of the United States of America	1,873	12.779	Q1
6	American Journal of Medical Genetics Part A	22	2.578	Q3	Science	1,662	63.832	Q1
7	Journal of the American Academy of Dermatology	21	15.487	Q1	Human Molecular Genetics	1,652	5.121	Q1
8	American Journal of Dermatopathology	19	1.319	Q4	Cell	1,318	66.85	Q1
9	Journal of Cutaneous Pathology	19	1.458	Q4	Oncogene	1,191	8.756	Q1
10	Proceedings of the National Academy of Sciences of the United States of America	16	12.779	Q1	Stem Cell Research & Therapy	1,122	8.088	Q1

JCR, journal citation reports; Q, quartile in category.

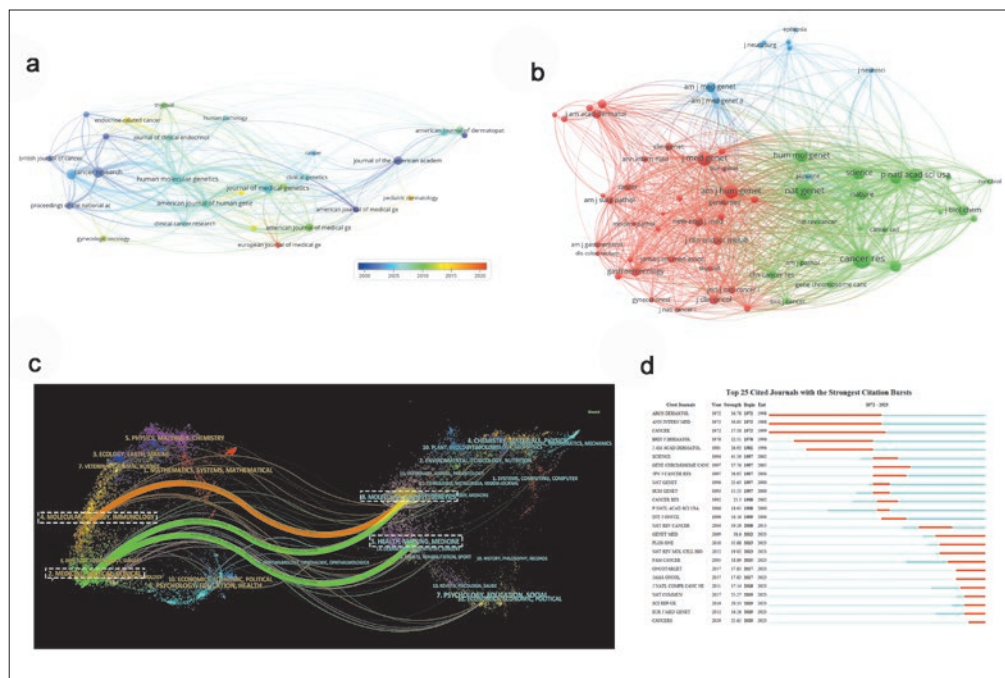


Fig 4 Analysis of journals and co-cited journals on Cowden syndrome. Network map of journals with more than 10 documents (a). Network map of journals with a minimum of 200 citations of a source (b). Dual map overlay of journals related to research on Cowden syndrome. The coloured paths indicate the relationships between journals on the left and cited journals on the right (c). The top 25 cited journals with the strongest citation bursts (d).

germline pten, pten hamartoma tumour syndrome and mutations had outbreak citations most recently, which indicated that the link between cowden syndrome and pten might be a research hotspot in the future.

Discussion

This bibliometric analysis research draws scientific knowledge maps of Cowden syndrome from 1972 to 2023. In the past 20 years, the number of publications has continued to fluctuate with a narrow range, indicating the stable output in this field. The USA was the most productive country (831 publications), accounting for more than half of all the articles. The USA also showed the strongest total link strength (377), followed by England (229), suggesting close cooperation with other countries. This situation was to some degree beneficial to the advancement of the research field. From the perspective of study institutions, all the top four institutions were in the USA, namely Ohio State University, Case Western Reserve University, Cleveland Clinic and Harvard University. Taken together, these results suggest that the USA plays a leading role and influences the direction of research in this field.

With regard to authors, Eng made the largest contribution with 190 publications, far more than the next most prolific authors, Meter (27) and Zhou (20). Eng was also in the top five co-cited authors. These data indicate their great contributions to the progression of this field. In 1997, Eng published the article “Germline

mutations of the *PTEN* gene in Cowden disease, an inherited breast and thyroid cancer syndrome” in Nature Genetics, which showed the highest number of citations.¹¹ In this study, they identified the mutations of the *PTEN* gene in patients with Cowden syndrome for the first time, and proved that *PTEN* acted as a tumour suppressor gene in the germline and played a role in organising the relationship between different cell types within an organ during development.

Analysis of the top 10 most productive journals showed 70% ranked Q1 and 4 journals had an IF greater than 10, including Cancer Research (IF₂₀₂₁ = 13.312), American Journal of Human Genetics (IF₂₀₂₁ = 11.043), Journal of the American Academy of Dermatology (IF₂₀₂₁ = 15.487) and Proceedings of the National Academy of Science of the United States of America (IF₂₀₂₁ = 12.779). The results indicated that literature on Cowden syndrome is mainly published in high IF journals, and this literature was vital to reflect the overview of research in the field. It is worth noting that the literature about Cowden syndrome in its initial stage from 1972 to 1998 were mainly published in skin-related journals, such as Archives of Dermatological Research, British Journal of Dermatology and Journal of the American Academy of Dermatology. This might be due to the fact that cutaneous and mucosal lesions are the most consistent findings in patients with Cowden disease. More recently, literature has been mainly published in gene-related journals, such as Genes, Chromosomes & Cancer, Nature Genetics and Human Genetics, because

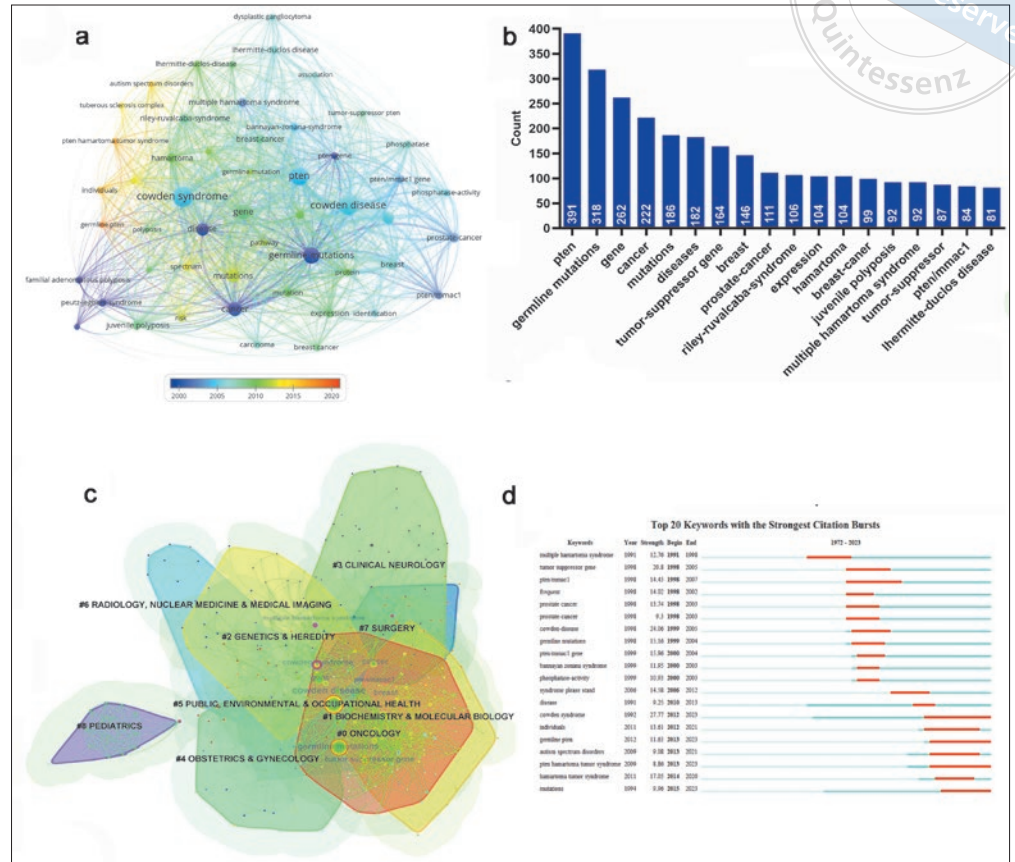


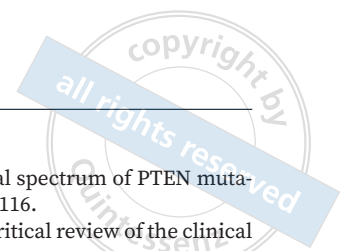
Fig 5 Analysis of keywords on Cowden syndrome. Distribution of keywords according to average publication year (blue, earlier; red, later) (a). Mapping of keywords more than 80 counts (b). Category cluster analysis of keywords (c). Top 20 keywords with the strongest citation bursts (d).

in 1997, Eng found that it was the *PTEN* mutations that caused this syndrome.¹¹ The mutation of *PTEN*, a tumour suppressor gene, greatly elevated the incidence of tumours in different organs, which has led researchers to focus mainly on Cowden syndrome/*PTEN* hamartoma tumour syndrome. Thus, the literature nowadays is published mainly in cancer-related journals, such as *Familial Cancer*, *Oncotarget*, *JAMA Oncology*, *Journal of the National Comprehensive Cancer Network* and *Cancers*.

Keywords reflect the central theme of publications and could provide core information of research frontiers. Initially, researchers were mainly focused on the clinical syndrome with keyword “multiple hamartoma syndrome” in strong citation from 1991 to 1998. With the identification of *PTEN* mutation in Cowden syndrome by Eng in 1997, keywords then shifted to “tumour suppressor gene”, “*pten/mma1*” and “germline mutations”, which resulted in research on Cowden syndrome being mainly focused on its pathogenesis. In addition, germline mutations, cancer and breast are also closely associated with Cowden syndrome. The majority of patients with Cowden syndrome (80%) had germline mutations in the *PTEN* gene.¹² The *PTEN* gene located

on chromosome 10q22-23 is a tumour suppressor via its lipid phosphatase activity negatively regulating the phosphatidylinositol 3-kinase (PI3K) pathway, inhibiting cell survival.^{13,14} The loss/reduction of function of *PTEN* results in activation of the PI3K/AKT/mTOR pathway, producing the opposite effect, including cell growth, protein synthesis and cell cycle progression, and ultimately manifesting as tumours. Germline mutations in the gene of *SDHB*, *SDHD* have been found for the minority of patients with Cowden syndrome without *PTEN* mutation.¹⁵

Cowden syndrome is part of PHTS, a disorder that primarily involves hamartomatous growths and cancers in multiple organs, especially the breast and thyroid.^{16,17} Nearly 85.2% of the affected female individuals could suffer from breast cancer, with age at diagnosis ranging from 38 to 46 years.¹⁸ The primary histological manifestation of breast cancer in Cowden syndrome is ductal adenocarcinoma uniquely surrounded by dense hyalinised collagen.¹⁹ Thyroid carcinoma is the second most common cancer in Cowden syndrome.²⁰ The literature reports that the lifetime risk of thyroid cancer in Cowden syndrome is up to 38%, with the mean age for diagnosis at 32 years old.²¹ Histopathologically,



follicular or papillary cancer are common types of thyroid cancer in Cowden syndrome.²² Apart from breast and thyroid cancer, the risk of endometrial, renal and glial malignancies in patients with Cowden syndrome appears to be increased, but has not been quantified.

Several shortcomings still remain in this study. For example, all the relevant publications were only downloaded from the WOS database and the latest publications after 6 May 2023 were not included, which might have led to some relevant publications being missed out and thus make the analysed publications incomplete.

Conclusion

The present authors first performed a systematical bibliometric analysis of research on Cowden syndrome to help scholars visualise the current research status. Although there are certain limitations to the present study, it still offers value, providing researchers with an intuitive and specific understanding of the field and helping to track research trends in a timely manner.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Qiao PENG contributed to the study design, data collection, analysis and manuscript draft; Drs Ning DUAN, Xiang WANG and Wen Mei WANG contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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