Global Research on Hereditary Hearing Impairment Over the Last 40 Years: A Bibliometric Study

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BACKGROUND: Research on hereditary hearing impairment has had several boosts to identify deafness-causing genes. The number of studies regarding the diagnosis and treatment modalities of hereditary hearing impairment is enormous and increasing; however, little or no research has been conducted for evaluating the development of scientific output and trends in the field. Here, we provide a comprehensive overview of centers that focus their research on hereditary hearing impairment and their scientific output.

METHODS: Bibliometric analysis of the publications related to hereditary hearing impairment published between 1980 and 2019 were used in this study, which were also indexed in Web of Science database.

RESULTS: The highest number of scientific articles on hereditary hearing impairment came from the United States, and it was also the most cited country. The University of Iowa is a leading center in the domain of hereditary hearing impairment in the world over the last 40 years. Fudan University, Central South University, and Harvard Medical School are also institutions that have had a focus on hereditary hearing impairment.

CONCLUSIONS: There is a progressive increase in scientific papers on hereditary hearing impairment over the last 40 years that we have found in our bibliometric study. We identified key centers in the scientific research on hereditary hearing impairment in the world and also key journals that focus on hereditary hearing impairment. This information can facilitate new researchers in this field to seek collaboration with experienced partners, better synthesize the orientation and boundaries of the subject, and find target journals. Ultimately, we provided a certain benchmark value for key centers that perhaps should have a more prominent role in constructing experimental research or even clinical guidelines.

KEYWORDS: Bibliometric analysis, genetic deafness, hereditary, hereditary hearing loss, publication

INTRODUCTION

One in every 500 newborns has congenital or prelingual hearing loss with a severity that will affect language development.1 In at least 50%, a genetic etiology can eventually be identified. Roughly 25% can be attributed to acquired etiologies like infections, and still a large portion remains of unknown origin. Hereditary hearing impairment (HHI) can be classified in different ways based on the identified locus of the gene defect, inheritance pattern, age of onset, audiological, and clinical phenotype.2

The research field of HHI has had several boosts to find deafness-causing genes. The first technological tool was of course the clinical use of the audiometer to determine which family members had hearing loss, perhaps mildly, and which family members had normal hearing. Then, classic linkage analyses with genetic markers and logarithm of the odds score have performed very successfully.3 In the 90s, almost all autosomal-dominant deafness genes were located or even identified. Already at that time, there was a growing gap between clinical application and the presence of this scientific genetic knowledge because the amount of information was too large to teach to general ENT surgeons and audiologists.4 Only dedicated clinical researchers were aware of the necessity to report genotype–phenotype correlations to enable clinicians to counsel their patients accordingly. Additionally, from family linkage analyses, the first leap was made to population genetics with single-nucleotide polymorphisms and large bio databases were constructed.5 Then, of course, next-generation sequencing (NGS) of the genome6,7 or even whole-genome sequencing...
Bibliometrics enables us to see the big picture of the current research through interpreting the evolution, distribution, and development of a certain field. Besides objective and reliable analyses like the change in research subjects and most investigated topics, they also provide the most producible scientists and institutions. It is necessary to analyze the current status of the research in the literature regarding HHI. There is a clear need for more research groups and more focused centers that conduct research on HHI. The result presented here can be a guideline in looking for collaboration partners and foresee insights for target journals and trends on HHI.

MATERIALS AND METHODS

Data were retrieved from the Web of Science (WoS) database that is provided by the Thomson Reuters Institute for Scientific Information. On October 24, 2020, we used the WoS database to gather academic publications on HHI from 1980 to 2019. We obtained, using the R bibliometrix package, the meta-data in the WoS citations on the full search results. The search query was “hereditary hearing impairment” OR “genetic deafness” OR “hereditary hearing loss” OR “sensory hearing loss of genetics origin.” The Boolean operator ‘OR’ joined the terms together, and all studies including 4 topics searched in an advanced search of WoS were reached. First, the Science Citation Index-Expanded category was selected in the index section of the search. Then, 101 publications (5628 citations), followed by Harvard University with 4306 institutions. Iowa University was the leading institution with 101 publications (5628 citations), followed by Harvard University with 4306 publications and 7199 citations (5.56%). China had the second place with 505 publications (12.68%) with 9895 citations (7.53%). The U.K. had the third place with 402 publications (10.10%) with 25913 citations (19.75%). Germany had the fourth place with 353 publications (8.87%) with 15573 citations (11.87%), and Japan had the fifth place with 309 publications (7.76%) with 8899 citations (6.78%). The top 10 of the lists consisted of the United States, China, Japan, and European countries. The top 25 list is formed by the other Asian countries like Japan, Israel, Iran, Turkey, South Korea, Pakistan, India, Taiwan, and only one African country, which is Tunisia. Collaboration map of the mostly published 25 countries is given in Figure 3.

RESULTS

After the exclusion criteria, it was determined that there were 3982 publications on HHI in the WoS database between 1980 and 2019, and total citations of articles were 131,236. The distribution of articles and citations by years are shown in Figure 2. A total of 3982 manuscripts were cited 131,236 times. H-index of these manuscripts was found to be 146, and the average number of citations was 32.96. Among 3982 publications related to HHI, we analyzed the first 25 articles with the most citations in the last 40 years (Table 1). In addition to that, the 10 most cited articles of 3982 articles related to HHI in the last 40 years are shown in Table 2.

Identified publications originated from 105 different countries/regions. The United States had the highest number with 1376 publications (34.56%) with 65,948 citations (50.25%), and China had the second place with 505 publications (12.68%) with 9885 citations (7.53%). The U.K. had the third place with 402 publications (10.10%) with 25,913 citations (19.75%). Germany had the fourth place with 353 publications (8.87%) with 15,573 citations (11.87%), and Japan had the fifth place with 309 publications (7.76%) with 8,899 citations (6.78%). The top 10 of the lists consisted of the United States, China, Japan, and European countries. The top 25 list is formed by the other Asian countries like Japan, Israel, Iran, Turkey, South Korea, Pakistan, India, Taiwan, and only one African country, which is Tunisia. Collaboration map of the mostly published 25 countries is given in Figure 3.

These articles were published in 859 different journals. International Journal of Pediatric Otorhinolaryngology was found to be the leading journal with 200 manuscripts followed by PloS One with 105 manuscripts and American Journal of Medical Genetics Part A with 100 manuscripts. The top 25 journals with the most articles published are given in Figure 5A.

The distribution of the first 25 institutes for the last 10 years in numbers of articles on HHI is shown in Figure 4B. Institutes that have been more active in the last 10 years are shown by the yellowing of the circles in Figure 4B. Before 2014, the University of Iowa, Harvard University, Institut Pasteur, Antwerp University, and Baylor College of Medicine were more active. Besides, in the last 4 years, Fudan University, Central South University, and Harvard Medical School seem to be more active in terms of research on HHI.

When we evaluate the annual number of articles on HHI (Figure 1), we can see that the studies of the institutes have increased significantly.
since 1990. The contribution of each institute on this subject changes over the years. While some institutes have produced articles on HHI earlier, some institutes appear to have been more active in recent years. The distribution of the first 25 journals for the last 15 years in terms of the production of articles on HHI is shown in Figure 5B. The journals that have been more active in the last 5 years are shown by the yellowing of the circles on the Figure 5B. Before 2010, American Journal of Human Genetics, Journal of Medical Genetics, and American Journal of Medical Genetics were more active, but our results show that PloS One and BMC Medical Journals have been more active in publishing articles on HHI in the last 5 years.

Using the VOSviewer software, it was found that there were 6199 different relevant keywords in these articles. The most commonly used keywords are deafness (464 times), hearing loss (392 times), and gjb2 (196 times). The most commonly used 20 keywords used at least 40 times on HHI during 1980-2019 are given in Figure 6A. The keywords were classified into 4 clusters shown as 4 kinds of colors, based on their co-occurrence relations. The cluster was deafness-related, including mostly “hearing loss,” “usher syndrome,” and “genetics,” and the cluster was GJB2-related, including mostly “Connexin 26,” “SLC26A4,” and “non-syndromic hearing loss.”

A network visualization map for trends based on keyword analysis used at least 35 times on HHI during 2000-2020 is given in Figure 6B. The keywords in blue color appeared early, and keywords in yellow color appeared recently. In the early stage, keywords related to “deafness,” “genetics,” and “cochlea” were the popular hotspots. However, recent research trends indicated that the keywords “next-generation sequencing,” “non-syndromic hearing loss,” and “SLC26A4” have recently attracted more attention from scholars.

**DISCUSSION**

Bibliometric analysis published in the field of otology in 2017 indicates that there has been a rapid increase in the total number of articles published in the field of otology in the last few decades, and among these, an increase has been shown in the number of articles related to cochlear implants and hearing aids after the 1990s. Emerging treatment options have popularized the domain of otology and raised the number of papers in otology. Although abrupt growth patterns were related to technological improvements or better yet disruptive technologies, this could not be substantiated in our data. We have found a rather gradual growth of the number of articles and citations about HHI since 1990, which in turn have led to an increase in the number of journals indexed in the WoS database. The concept of inheritance as a cause of deafness was accepted in the last quarter of the 19th century. Then, it was aimed to identify the non-syndromic deafness genes in 1995. Since the introduction of human genome mapping, and human and mouse genome structures in an attempt to assess hereditary diseases in the 1990s, studies on HHI have also increased after 1990. In addition, Sanger et al have developed the termination and fragmentation methods for sequencing DNA. DNA sequence
production has been carried out almost entirely by semi-automatic applications of Sanger biochemistry since the early 1990s. We believe that, as a result of the intensification of the researches on the subject, the articles on HHI have increased since 1990.

In addition, the significant peak in the number of articles in the 1990s, a continuous increase was also evident between 2010 and 2015 as shown in Figure 2. That increase seems to be influenced by the revolutionary approaches of new gene identification such as NGS and WGS. For screening, linked loci containing hundreds of genes can be subjected to parallel sequencing of all linked genes or custom targeted capture and massive parallel sequence of a single locus to reduce the need to design customized panels. In small families, single-gene screening has been provided by using NGS-supported methods like WGS. By using these approaches, 21 non-syndromic hearing loss genes were successfully identified between 2010 and 2015. DNA diagnostics have become so powerful to find mutations that mutation classification systems are needed to predict their pathogenicity. The report of the American College of Medical Genetics and Genomics proposes standard terminology to describe the variants identified in Mendelian disorders. Actually, these kinds of strategies show the lack of genotype–phenotype correlation studies and underline the gap between clinicians and researchers.

When the international cooperation network and publication number of HHI-related articles have been analyzed worldwide, the United States is the country possessing most of the research partnerships and collaboration articles, which is followed by China. The increase in the production of these 2 countries can be attributed to the allocation of more research funds, or in other words, the National Institutes of Health in the United States invested almost $30 billion in medical research in 2014. However, more than 50% of congenital hearing losses affecting at least 1 in every 500 new births are genetic in origin, and the cost of hearing loss to society in the United States is approaching billions of dollars. Therefore, the intensified research on HHI in the United States may end up with the benefit of the patients from modern sequencing technologies and advanced gene therapy treatment methods. It is worthy to note that the Chinese economy has steadily increased research and development spending over the past 3 decades. Low country collaboration contributions from developing countries, including countries in Africa, have been associated with a high frequency of researchers characterized by self- or independent studies. In this context, Tunisia is the only African country with the least number of articles (43 publications) and the lowest number of citations (715 citations) among the first 25 countries. We consider that international cooperation resources offered to researchers can be brought together with researchers in those countries and solved by more effective use.

When we evaluate the contribution of the institutes in the articles on HHI, we see that there are results parallel to those in the countries. Three of the top five universities are universities in the
Table 1. Top 25 Articles on HHI With the Most Citations

| Title                                                                 | Author(s)                         | Journal               | Year | TC   | AY    |
|----------------------------------------------------------------------|-----------------------------------|-----------------------|------|------|-------|
| 1 Connexin 26 mutations in hereditary non-syndromic sensorineural deafness | Kelsell et al16                  | Nature                | 1997 | 1045 | 43.54 |
| 2 Mitochondrial DNA mutations in human disease                        | Taylor and Turnbull35            | Nat Rev Genet         | 2005 | 993  | 62.06 |
| 3 Mutation in mitochondrial transfer RNA (UUR) gene in a large pedigree with maternally transmitted type II diabetes-mellitus and deafness | van den Ouweland et al36         | Nat Genet             | 1992 | 904  | 31.17 |
| 4 Structural and functional diversity of connexin genes in the mouse and human genome | Willecke et al18                 | Biol Chem             | 2002 | 877  | 46.16 |
| 5 Mitochondrial ribosomal-RNA mutation associated with both antibiotic-induced and non-syndromic deafness | Prezant et al32                  | Nat Genet             | 1993 | 857  | 30.61 |
| 6 Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS) | Everett et al25                  | Nat Genet             | 1997 | 816  | 34    |
| 7 Defective Myosin VIIa gene responsible for usher syndrome type 1b  | Weil et al27                     | Nature                | 1995 | 787  | 30.27 |
| 8 Skeletal overgrowth and deafness in mice lacking fibroblast growth factor receptor 3 | Colvin et al21                   | Nat Genet             | 1996 | 687  | 27.48 |
| 9 Genetic epidemiology of hearing impairment                          | Morton30                         | Ann N Y Acad Sci      | 1991 | 684  | 22.8  |
| 10 Auditory neuropathy                                               | Starr et al34                    | Brain                 | 1996 | 680  | 27.2  |
| 11 Rare variants create synthetic genome-wide associations            | Dickson et al31                  | PLoS Biol             | 2010 | 635  | 57.73 |
| 12 Cockayne syndrome - review of 140 cases                            | Nance and Berry 31              | Am J Med Genet        | 1992 | 538  | 18.55 |
| 13 A type-VII myosin encoded by the mouse deafness gene Shaker-1     | Gibson et al26                   | Nature                | 1995 | 497  | 19.12 |
| 14 A genome-wide search for human non-insulin dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2 | Hanis et al27                   | Nat Genet             | 1996 | 495  | 19.8  |
| 15 Gap junctions: structure and function (Review)                    | Evans and Martin 24             | Mol Membr Biol        | 2002 | 494  | 26    |
| 16 Connexin-26 mutations in sporadic and inherited sensorineural deafness | Estivill et al15                 | Lancet                | 1998 | 485  | 21.09 |
| 17 Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene | Denoyelle et al14               | Hum Mol Genet         | 1997 | 484  | 20.17 |
| 18 Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males | MacDermot et al38              | J Med Genet            | 2001 | 471  | 23.55 |
| 19 Connexin26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans | Zelante et al17                | Hum Mol Genet         | 1997 | 457  | 19.04 |
| 20 Patient-specific induced pluripotent stem-cell-derived models of LEOPARD syndrome | Carvajal-Vergara et al26         | Nature                | 2010 | 455  | 41.36 |
| 21 A clinical-study of Type-2 neurofibromatosis                      | Evans et al23                   | Q J Med                | 1992 | 448  | 15.45 |
| 22 Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion | Royaux et al23                 | Proc Natl Acad Sci USA | 2001 | 396  | 19.8  |
| 23 Mutations in the connexin 26 gene (GJB2) among Ashkenazi Jews with nonsyndromic recessive deafness | Morell et al23                 | N Engl J Med          | 1998 | 396  | 17.22 |
| 24 Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist | Hoffman et al18               | Lancet                | 2004 | 394  | 23.18 |
| 25 The Mouse Snells Waltzer Deafness Gene encodes an unconventional myosin required for structural integrity of inner-ear hair-cells | Avraham et al19                | Nat Genet             | 1995 | 383  | 14.73 |

HHI, hereditary hearing impairment; TC, total citations; AY, average per year.
United States. Besides the availability of support funds, economic strength, and research facilities,\textsuperscript{56,57} this productivity can be attributed to a high level of national and international collaboration with other institutions that can affect research visibility and citation frequency.\textsuperscript{58} In a bibliometric analysis that evaluated the relationship between the University–Industry in the United States published in 2016, it has been emphasized that the universities have high-quality research environments with strong research ties with the industry and that large research universities with strong ties to the domestic industry play critical roles.\textsuperscript{59} When sufficient financial and technological support is combined with a trained workforce, it is seen that a lot of quality and quantity studies have emerged. Bibliometric studies provide very valuable results to scientists in terms of objectively determining the institutes that have studies on HHI and analyzing the cooperation between these institutes. As a result, young researchers will know where to apply. Therefore, these active institutes can continue to play an active role in future research, and it would be fruitful for researchers to consider selecting them as partners.

Callaham et al\textsuperscript{60} stated that the original journal impact factor has been the strongest predictor of annual citations rather than the methodology or quality of the research. They suggest that these citations may be more strongly influenced by the publication journal’s reputation than by the design value of the work. The most important journals in a particular field of research can be determined by

### Table 2. The Top 10 Cited Articles of 3962 Articles on HHI

| Title                                                                 | Author(s)          | Journal              | Y   | TC  |
|----------------------------------------------------------------------|--------------------|----------------------|-----|-----|
| 1 Connexin 26 mutations in hereditary non-syndromic sensorineural deafness | Kelsell et al\textsuperscript{16} | Nature | 1997 | 373 |
| 2 Genetic epidemiology of hearing impairment                          | Morton\textsuperscript{10}   | Ann N Y Acad Sci | 1991 | 339 |
| 3 Newborn hearing screening—a silent revolution                      | Morton et al\textsuperscript{4} | New Engl J Med | 2006 | 290 |
| 4 Connexin-26 mutations in sporadic and inherited sensorineural deafness | Estivill et al\textsuperscript{12} | Lancet | 1998 | 235 |
| 5 Connexin26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans | Zelante et al\textsuperscript{17} | Hum Mol Genet | 1997 | 224 |
| 6 Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene | Denoyelle et al\textsuperscript{13} | Hum Mol Genet | 1997 | 223 |
| 7 A deletion involving the connexin 30 gene in nonsyndromic hearing impairment | del Castillo et al\textsuperscript{10} | N Engl J Med | 2002 | 205 |
| 8 Mutations in the connexin 26 gene (GJB2) among Ashkenazi Jews with nonsyndromic recessive deafness | Morell et al\textsuperscript{22} | N Engl J Med | 1998 | 199 |
| 9 GJB2 mutations and degree of hearing loss: a multicenter study       | Snoekx et al\textsuperscript{41} | Am J Hum Genet | 2005 | 191 |
| 10 Novel mutations in the connexin 26 gene (GJB2) that cause autosomal recessive (DFNB1) hearing loss | Kelley et al\textsuperscript{40} | Am J Hum Genet | 1998 | 190 |

HHI, hereditary hearing impairment; Y, year; TC, total citation.

![Figure 3. Network visualization map for an international collaboration of the top 25 countries on HHI during 1980-2019 (the size of the circle correlates with a larger number of publications; thick lines indicate strong relationship and colors indicate cluster idem). HHI, hereditary hearing impairment.](image)
analyzing article distribution, and researchers can use these findings to decide which journal to submit to. The number of articles published in a particular journal may be considered as a measure of the importance or “weight” of that journal for a particular research subject or area. When researchers find the right and high-quality journal that fits their subject, they will gain a great deal of time and citations from other colleagues who are interested in that topic. For this reason, the network analysis of productive journals in our study on HHI is an objective guide. Experts in the field may have known which journal to choose, but our data here are available for junior researchers to perhaps guide their choice.

Citations are highly correlated with peers’ views on an indicator of academic success for authors and journals and a scientist’s contribution to his field. Therefore, citations complement the publication chain and form the basis of the development of scientific publications. Articles with the largest number of citations have far-reaching effects on the development and trend of a particular field, as they provide the basis for future studies. The more recent studies are likely to cite the first game-changing publication containing a novel mutation or often novel genotype-phenotype correlation with high clinical importance. Evaluation of the most cited articles is very valuable in terms of accessing quality articles on that subject. The top 25 articles on HHI with the most citations and the first 10 articles cited by 3982 articles about HHI are valuable information to guide the researchers who want to write articles on this subject.

Keywords provide a reasonable description of research hotspots. Hot topics can be defined by a number of citations or word frequencies, as well as indicate not only the current research focus areas or hotspots but also potential trends of the research area. Analyzing and evaluating the keywords in the articles...
is important in terms of knowing the boundaries of the subject. Authors select and use keywords that will stand out in their articles. Since these words can be easily obtained with the bibliometric analysis method for a research topic, the important points of the subject are scanned.67 The frequency and use of HHI-related keywords in Figure 6A will give an idea to researchers who want to do research in terms of determining the important points of their studies. One of the most frequently used keywords is “GJB2” because of a mutation in the Gap junction protein beta 2 (GJB2) gene, one of the most common causes of autosomal recessive genetic hearing loss worldwide.68 Since it is a relatively small gene, it has been excessively studied and found to encounter many deafness-causing mutations. Despite the great interest in the GJB2 gene as a potential target for gene therapy, germline mutations in mouse GJB2 seem difficult due to death in utero,69 but due to ongoing active studies on this topic, it is among the most frequently used keywords in articles related to HHI. Since more than 100 different genes that cause genetic hearing loss have been identified, each unique cause will need to be characterized and evaluated for its potential to be the target of successful gene therapy intervention.52 Notwithstanding all these difficulties, we suggest that HHI-related comprehensive bibliometric analyses like presented here will be useful for the limitations and trends of the subject while the field of gene therapy develops novel and effective treatments for patients with genetic hearing loss.

Bibliometric analysis is a powerful approach to predict trends in research activity using literature databases and literature features.70 Not surprisingly, many screening programs for genetic hearing loss contain screening for Cx26 and SLC26A4 mutations. In addition to determining the most used keywords, determining the recently used keywords enables the trend points of the subject to be revealed. When we evaluate the usage distribution of keywords in the last 20 years in the articles about HHI, we see that “next-generation sequencing” and “SLC26A4” are more trendy in the last 10 years. The SLC26A4 (PDS gene) gene was isolated by Everett et al25 in 1997 as the mutated gene in Pendred syndrome.71 From 1995 to 2002, molecular SLC26A4 screening was performed to determine the prevalence, spectrum, and genotype–phenotype correlations of SLC26A4 gene mutations in non-syndromic hearing loss and enlarged vestibular aqueduct pathologies as part of a national research program on deafness.72 In 2019, the first studies showing the feasibility of gene therapy for pendrin-related hearing loss were published.73 Secondly, cochlear implantation for deafness due to SLC26A4 gene mutations involves an intraoperative challenge referred to as “gusher” because of anatomical anomalies recognizable by an enlarged vestibular aqueduct on computed tomography images. Therefore, the trait is under the focus of researches of different domains, e.g., radiology, anatomy, and surgery increasing the number of publications and thus keywords. Another frequent keyword NGS, which has appeared in the last 10 years, has the potential to significantly accelerate the popularization of biomedical research on the comprehensive analysis of genomes, transcriptomes, and interactomes inexpensive.7 In recent years, NGS technologies have proven to be highly effective and powerful tools for population genetic studies on hearing loss.74 Noteworthy is that our data do not find a keyword referring to Clustered Regularly Interspaced Short Palindromic Repeats), but it can be expected to appear in the coming years of research on HHI.

Our analyses were based on articles reported in the WoS database. Therefore, data analysis is relatively objective and comprehensive. However, there are some limitations specific to the bibliometric methodology that we must acknowledge. Other medical literature databases Pubmed, Scopus, and Google Scholar were not used as different databases cannot be combined and analyzed together.

We show a progressive increase in scientific output in HHI in our bibliometric analyses here. Although very powerful and fast DNA sequencing strategies have been implemented in laboratories, these do not seem to have caused a disruptive increase in the scientific output for HHI. The increase is gradual over the last 40 years, and it seems to be centered on a limited number of countries and laboratories. Noteworthy is that a plateau of the growth is not seen nor to be expected with emerging technologies.
CONCLUSION
There is a gradual increase in scientific papers about HHI over the last 40 years. This seems to be independent of the implementation of disruptive technologies on faster DNA diagnostics. On one side, there is an increasing population with hearing problems, and on the other side, there is also an increasing gap between scientific knowledge on HHI and the translation of this knowledge into clinics. There is possibly a need for more genotype–phenotype correlation studies, more researchers, and more centers focusing together on resolving the burden of HHI. Networks, collaborations, institutions, and even individual researchers revealed here from our bibliometric study over the last 40 years can facilitate future research collaborations. At the same time, the revealed pioneering centers perhaps should also reach out and take a certain responsibility to define guidelines and protocols for the benefit of patients with HHI.

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