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Article

Bibliometric Analysis of Gene Research on Aging

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ABSTRACT

Aging is associated with various factors identified in the hallmark of aging. Numerous studies have been conducted to identify genes involved in the aging process, allowing for a comprehensive understanding of this phenomenon. This study aims to provide an overview of research on genes associated with the aging process. Data for this study was obtained and analyzed from the SCOPUS database covering the period from 2014 to 2024, with a focus on medicine, neuroscience, and nursing. The keywords used for the search were "gene," "longevity," and "aging." The search results were filtered to match the study's purpose and were limited to articles in English. The data obtained was analyzed using VOS viewer version 1.6.20. A total of 1,603 articles were analyzed. The highest number of publications occurred in 2021. The most frequent sources for these articles were the journals *Biogerontology* and *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. The United States was the leading contributor in publications (n=488), with Harvard Medical School producing the highest number (n=45). The most-cited article was by Loboda in 2016 (1,863 citations). Research on genes associated with aging has shifted from identifying genes (2017-2019) to focusing on the functions of these genes in physiological processes and other risk factors of aging. In conclusion, the aging research has evolved from focusing solely on gene identification to exploring the physiological functions and risk factors related to aging.

INTRODUCTION

The aging process is often associated with the onset of various diseases. Research in the field of molecular biology summarizes various aging factors in the hallmark of aging. The trend in aging research focuses on epigenetic processes[1]. Genetic factors contribute 15%-40% to lifespan length. Lifespans of over 90 years are also influenced by environmental factors, which are more commonly observed in men[2]. Some studies have examined the role of single nucleotide polymorphisms (SNPs) in the FOXO3 gene, which is associated with a long and healthy lifespan[2,3]. In addition, another gene, Sirtuin 1 (SIRT1), can protect cells from oxidative stress, regulate fat/protein metabolism, and enhance DNA stability[4]. Another gene thought to influence lifespan

through cardiovascular system responses is BPIFB4[5]. In recent years, research has expanded to not only focus on genes related to aging but also those that affect healthy conditions in old age[6]. This study was conducted to provide an overview of genetic research related to the aging process.

METHODS

This research utilized SCOPUS as the database for sourcing articles. The search strategy involved filtering article titles, abstracts, and keywords with the terms "gene AND longevity AND aging." The articles included in the search were from 2014 to 2024, focusing on the fields of medicine, neuroscience, and nursing. The types of articles sought were research articles and reviews, with keyword restrictions such as longevity, aging, article, human, animals, animal, humans, lifespan, male, female, gene expression, gene, mouse, cell aging, animal model, gene mutation, single nucleotide polymorphism, senescence, life extension, growth, development and aging, genetic association, transcription factor, genetic variability, age, gene overexpression, DNA methylation, physiological stress, mutation, sirtuin, cellular senescence, aging, transcription factor Foxo (is kind of transcription factor that have important roles in metabolism, cellular proliferation, stress resistance, and apoptosis), antiaging activity, sex differences, epigenetics, genetics, in vivo study, gene expression profiling, mice, inbred C57BL, gene function, klotho protein, and microRNA. Only articles written in English were used. The information collected from the articles included the number of publications each year, keywords, author names, affiliated universities, and the country where the research was conducted. The data was analyzed using VOS viewer 1.6.20.

RESULTS

Based on the search criteria, 1,603 articles were retrieved from SCOPUS. According to the data in Figure 1A, the United States ranked as the top country for publications on genes and aging, with 688 articles, followed by China (n = 240) and Germany (n = 151). The United Kingdom ranked fourth with 146 publications, followed by Italy with 135 articles, and Japan with 88 articles. Spain ranked seventh, followed by India, France, and Canada. Over the years 2014–2024, the ten journals with the highest number of publications on gene research in aging were *Biogerontology* (n = 80), *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* (n = 80), *Geroscience* (n = 77), *eLife* (n = 69), *PLOS Genetics* (n = 64), *Ageing Research Reviews* (n = 43), *Frontiers in Genetics* (n = 41), *Rejuvenation Research* (n = 32), *Nature Aging* (n = 29), and *Nutrients* (n = 28). Based on author affiliation, Harvard Medical School ranked highest with 45 articles, followed by the University of Washington with 40 articles, and the Albert Einstein College of Medicine with 36 articles. Rankings four through ten were, respectively, the Chinese Academy of Sciences, Ministry of Education of the People's Republic of China, National Institutes of Health, Alma Mater Studiorum

Università di Bologna, University of Southern Denmark, Max Planck Institute for Biology of Ageing, and Inserm.

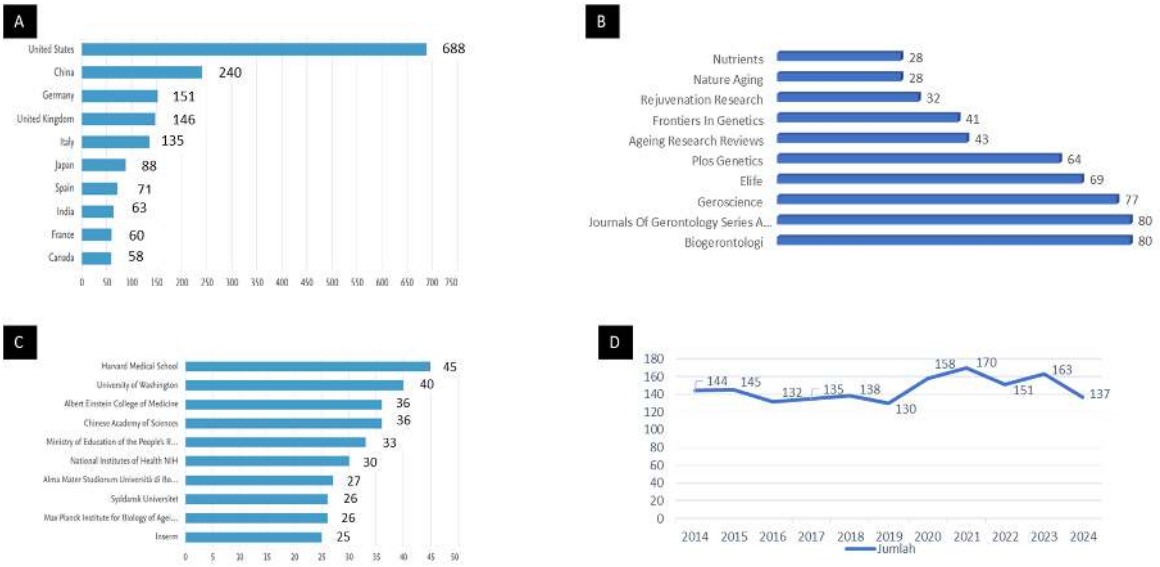

Figure 1 showing the characteristics of gene research on aging. A: Ten countries with the highest number, B: The top 10 journals by the number of publications, C: The top 10 affiliations with the most publications in this research area. D: showing the annual number of publications from 2014 to 2024.

The Table 1 presents the 10 most-cited articles in gene research on aging. The most highly cited article is by Loboda (2016) with 1,863 citations, followed by Hammond (2019) with 1,212 citations. Other articles have citation counts ranging from 326 to 685. This indicates that more recent research, such as Hammond (2019), remains highly influential, while some older studies also continue to have a significant impact.

Table 1. The 10 most-cited articles in gene research on aging

Author	***Year of Publication***	***Citation***
Loboda	2016	1863
Hammond	2019	1212
Newman	2014	685
Bale	2015	515
Gureev	2019	428
Blackwell	2015	404
colacurcio	2016	333
Hood	2017	326
Kim	2019	324
Cardoso	2018	319

The figure 2 presents keyword-based research data on aging, highlighting key themes and trends. In Panel A, the keywords are categorized into three main clusters: red represents risk factors, blue corresponds to metabolism-related research, and green focuses on genes involved in aging. This clustering helps identify the major areas of study within aging research. Panel B illustrates the research trends over time, with a color gradient indicating how the focus of studies

has evolved. The visualization provides valuable insights into the progression of aging research, emphasizing the importance of risk factors, metabolism, and genetic influences in understanding the aging process.

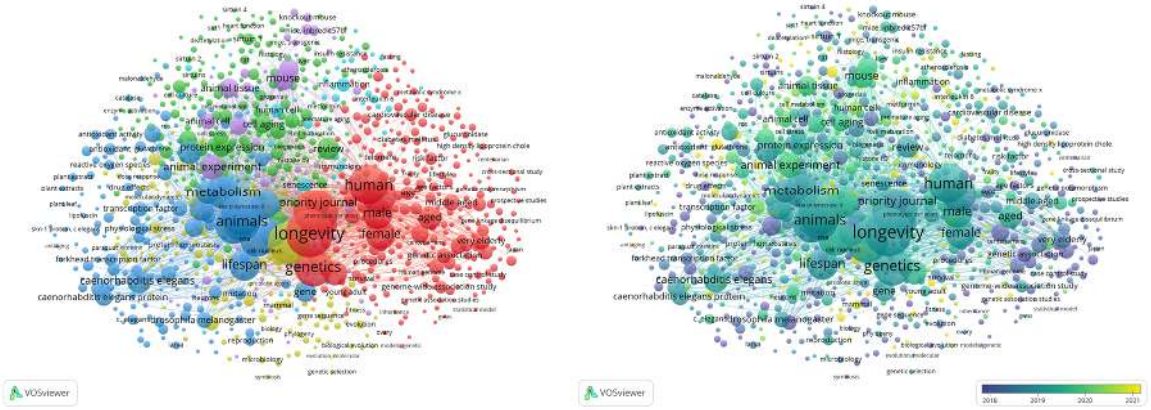

Figure 2. Data based on keyword of the research. A: Keyword divided into 3 clusters: Red related to risk factor, blue related to metabolism, and green related to genes involved in aging. B: Research trend related to aging

DISCUSSION

Aging is defined as the decline in cellular, tissue, and organ function, with an onset that varies among individuals. Aging is thought to be influenced by reactive oxygen species (ROS), which are byproducts of cellular activity[7]. Longevity is affected by both genetic and environmental factors, with genetics accounting for approximately 30% of the variability in lifespan[8]. Environmental and epigenetic factors are also increasingly considered to play significant roles. These factors interact and are linked to oxidative stress mechanisms and gene expression[9].

From 2014 to 2024, research on genes in aging has shown a steady increase, indicating growing interest among researchers in exploring aging-related information. Harvard Medical School is the university with the highest number of publications on gene research in aging. Four of the ten institutions with the most publications are from Europe, accounting for a total of 32.10% of publications. The journals with the highest number of publications reviewing genes in aging are *Biogerontology* and *The Journal of Gerontology Series A: Biological Sciences and Medical Sciences*. These two journals publish articles covering various aspects of aging research, including biochemical, molecular, demographic, and neurological perspectives. The most cited article is by Loboda, published in 2016 in *Cellular and Molecular Life Sciences*, with 1,863 citations.

The analysis using VOS viewer revealed three clusters. In the red cluster, several keywords are associated with risk factors, such as genetics, phenotypic variation, gender, diabetes mellitus, and cardiovascular disease. The green cluster includes keywords related to fundamental research involving genes like sirtuin 4, sirtuin 1, sirtuin 2, and deacetylation. In the blue cluster, keywords connect to bodily processes that influence aging, such as metabolism, drug effects, physiological

stress, mutase, and antioxidant activity. Recent developments in research have expanded previous genetic discoveries by incorporating gene modifications like gene knockdown, examining the roles of genes in cellular senescence, and exploring anti-aging activity in humans and other organisms. Additionally, other factors related to aging are now being investigated, including fasting, metabolic diseases (such as diabetes mellitus), and chronic diseases.

Sirtuin 1 (SIRT1), in addition to its role in longevity through cellular responses to oxidative stress, cellular senescence, and inflammation regulation, also plays a role in preventing disease progression[10]. Research on SIRT1 suggests that this gene contributes to reducing fat storage, mobilizing fatty acids in adipose tissue, and enhancing β-oxidation in the liver and muscles. SIRT1, along with forkhead transcription factors of class O (FOXO), nuclear factor-kappa B (NFκB), and p53, plays a protective role against aging and apoptosis[11]. Various genes and environmental factors interact in the aging process. *In silico* studies show an interaction between environmental factors that stimulate growth, aging, metabolism, and disease in living organisms[12]. Lifestyle is also believed to influence aging; for example, periodic fasting can alter metabolism by increasing β-hydroxybutyrate (BHB) and pyruvate dehydrogenase kinase isoform 4 (PDK4) expression in the blood, as well as boosting the expression of MtDNA, SIRT1, SIRT3, and miRlet7b-5p[13].

Besides genetics, Several SNPs in genes belonging to distinct pathways have been associated with the longevity phenotype. Genome-Wide Association Studies (GWAS) on human longevity conducted with diverse populations (including North America, Europe, and more recently, China) have largely been unsuccessful in uncovering new genetic factors related to lifespan. The only locus consistently associated with longevity across different populations has been TOMM40/APOE/APOC1. The pivotal role of TP53 may not be unexpected, as this gene is a well-established tumor suppressor involved in DNA damage response. It balances tumor surveillance with the preservation of stem cell populations, ultimately providing advantages for both cancer prevention and longevity. The antiproliferative function of TP53 which is crucial for tumor suppression could affect self-renewal function of stem/progenitor cells and contribute to aging[14,15].

Aging is an equally complex process, which is affected by a plethora of exogenous and endogenous factors, and which impacts virtually all crucial biological processes by a progressive loss of cellular functions. Circadian rhythms (CR) controlling a multitude of biological cycles and enabling an individual to adjust to periodic environmental changes during daytime, seasons, and lifetime. Expression of CR core genes and their downstream targets are responsible for age-related variations in CR regulation. Moreover, it is unclear to what extent these changes in CR gene regulatory patterns may overlap in distinct tissues and species. Longevity and aging may be influenced by, and in turn influence, both positive and negative mood and response to stress. Genes for involvement in mood disorders and stress disorders, is ANK3 indeed involved in

longevity/aging[16,17]. Dietary restriction (DR) refers to regimens including the reduction of the intake of either calories or of specific components of the diet, such as protein or certain amino acids, and to intermittent and periodic fasting (IF and PF, respectively), which may or may not require an overall reduction in calorie intake. Signaling pathways by which CR and PR extend lifespan include those activated by growth hormone, insulin-like growth factor-1 (IGF-1) and insulin, and involve downstream factors, including phosphoinositide 3-kinase (PI3K), mammalian target of rapamycin complex 1 (mTORC1), protein-kinase A (PKA), AMP-activated protein kinase (AMPK), per oxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), sirtuins and forkhead transcription factors (FOXOs), that are well established to regulate or affect aging and longevity[18].

CONCLUSION

The bibliometric analysis shows an increase in publications starting in 2019, peaking in 2021. Harvard Medical School has published the most articles related to genes and aging. *Biogerontology* and *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* are the journals with the highest number of publications on genes in aging. The most-cited article is by Loboda, published in 2016. Research on genes in aging is now expanding to explore the influence of environmental and lifestyle factors on the aging process.

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