Ahmad Dahlan Medical Journal
VOL 5, No. 2, 198-204
http:// http://journal2.uad.ac.id/index.php/admj

Article

Bibliometric Analysis of Gene Research on Aging

[1]Rachma Greta Perdana Putri*, [1]Annisa Annisa, [2]Ario Tejosukmono, [3]Dewi Yuniasih

Email (Corresponding Author) : * rachmagreta@med.uad.ac.id
[1]Department of Histology, Faculty of Medicine, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
[2]Department of Anatomy, Faculty of Medicine, Universitas Ahmad Dahlan, Yogyakarta, Indonesia
[3]Department of Public Health, Faculty of Medicine, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

ARTICLE INFO

Article history
Received 12 Nov 24
Revised 07 Des 24
Accepted 13 Des 24

Keywords

Age,
Aging
Bibliometric,
Gene,
Research

(consist of 3 to 5 keywords)

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.

tables, figures, or informative illustrations.

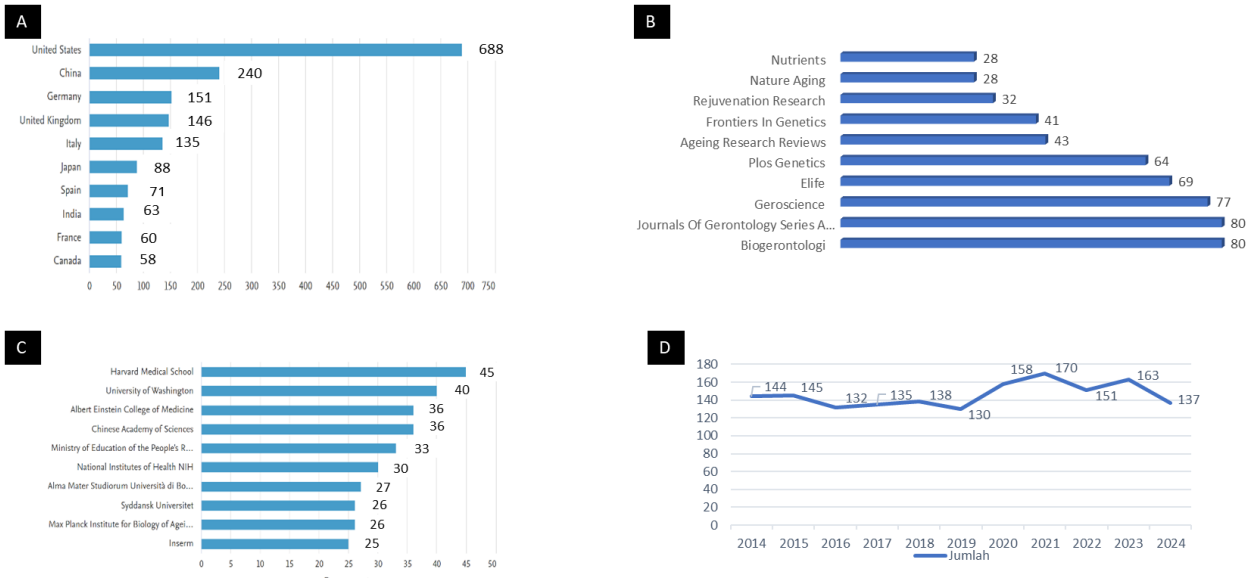

Figure 1 showing the characteristics of gene research on aging. A: Ten countries with the highest number, B: The top 10 journals by the number of publications, C: The top 10 affiliations with the most publications in this research area. D: showing the annual number of publications from 2014 to 2024.

Authors with highly cited articles are listed in Table 1. The keyword analysis based on VOS viewer is shown in Figure 3. Cluster 1 (Red) might include keywords like human, phenotypic variation, genetics, very elderly, etc. Cluster 2 (Blue) could feature keywords related to metabolic processes like *physiological stress, transcription factor, molecular dynamics, etc*. Cluster 3 (Green) should focus on specific genes such as *SIRT1*, *sirtuin4, cell aging*, etc.

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	2019c	324
Cardoso	2018	319

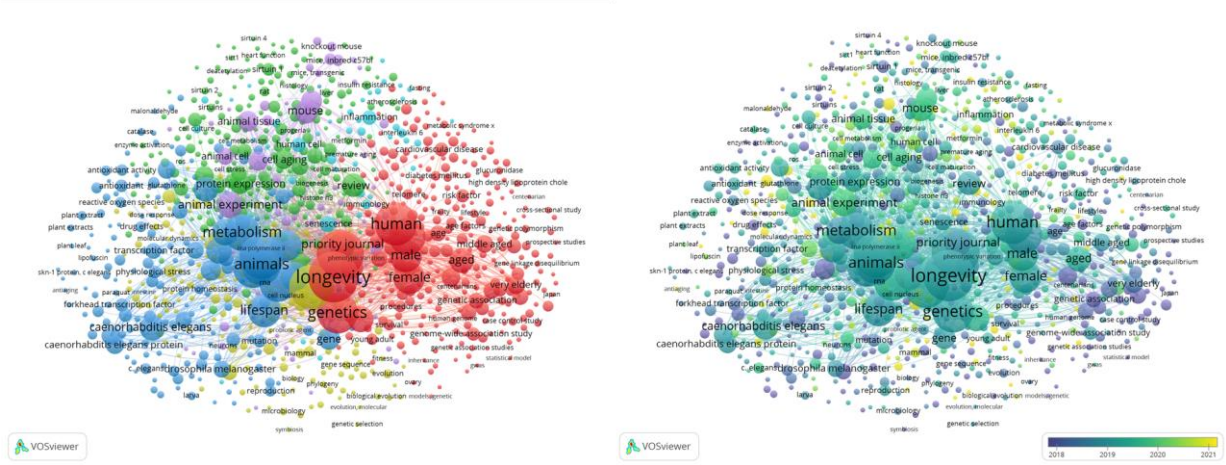

Figure 2. Data based on keyword of the research. A: Keyword divided into 3 clusters: Red related to risk factor, blue related to metabolism, and green related to genes involved in aging. B: Research trend related to aging

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 VOSviewer 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.

REFERENCES

1. Blankenburg H, Pramstaller PP, Domingues FS. A network-based meta-analysis for characterizing the genetic landscape of human aging. *Biogerontology*. 2018;19(1):81-94. doi:10.1007/s10522-017-9741-5
2. chen R, Morris BJ, Donlon TA, et al. FOXO3 longevity genotype mitigates the increased mortality risk in men with a cardiometabolic disease. *Aging*. 2020;12(23):23509-23524. www.aging-us.com
3. Donlon TA, Morris BJ, Chen R, et al. FOXO3 longevity interactome on chromosome 6. *Aging Cell*. 2017;16(5):1016-1025. doi:10.1111/acel.12625
4. Kilic U, Gok O, Erenberk U, et al. A remarkable age-related increase in SIRT1 protein expression against oxidative stress in elderly: SIRT1 gene variants and longevity in human. *PLoS One*. 2015;10(3). doi:10.1371/journal.pone.0117954
5. Cattaneo M, Aleksova A, Malovini A, et al. BPIFB4 and its longevity-associated haplotype protect from cardiac ischemia in humans and mice. *Cell Death Dis*. 2023;14(8). doi:10.1038/s41419-023-06011-8
6. Hepowit NL, Blalock E, Lee S, Bretland KM, MacGurn JA, Dickson RC. Reduced sphingolipid biosynthesis modulates proteostasis networks to enhance longevity. *Aging*. 2023;15(2):472-491. doi:10.18632/aging.204485

7. Gola F, Gaiaschi L, Roda E, et al. Voghera Sweet Pepper: A Potential Ally against Oxidative Stress and Aging. *Int J Mol Sci*. 2023;24(4). doi:10.3390/ijms24043782
8. Yerges-Armstrong LM, Chai S, O'Connell JR, et al. Gene Expression Differences between Offspring of Long-Lived Individuals and Controls in Candidate Longevity Regions: Evidence for PAPSS2 as a Longevity Gene. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*. 2016;71(10):1295-1299. doi:10.1093/gerona/glv212
9. Pereira Da Silva A, Costa MDC, Aguiar L, et al. Impact on Longevity of Genetic Cardiovascular Risk and Lifestyle including Red Meat Consumption. *Oxid Med Cell Longev*. 2020;2020. doi:10.1155/2020/1305413
10. Taka C, Hayashi R, Shimokawa K, et al. SIRT1 and FOXO1 mRNA expression in PBMC correlates to physical activity in COPD patients. *International Journal of COPD*. 2017;12:3237-3244. doi:10.2147/COPD.S144969
11. Curjuric I, Imboden M, Bridevaux PO, et al. Common SIRT1 variants modify the effect of abdominal adipose tissue on aging-related lung function decline. *Age (Omaha)*. 2016;38(3). doi:10.1007/s11357-016-9917-y
12. Sadria M, Layton AT. Interactions among mTORC, AMPK and SIRT: a computational model for cell energy balance and metabolism. *Cell Communication and Signaling*. 2021;19(1). doi:10.1186/s12964-021-00706-1
13. Lilja S, Stoll C, Krammer U, et al. Five days periodic fasting elevates levels of longevity related christensenella and sirtuin expression in humans. *Int J Mol Sci*. 2021;22(5):1-15. doi:10.3390/ijms22052331
14. Zhao Y, Wu L, Yue X, et al. A polymorphism in the tumor suppressor p53 affects aging and longevity in mouse models. Published online 2018. doi:10.7554/eLife.34701.001
15. Dato S, Soerensen M, De Rango F, et al. The genetic component of human longevity: New insights from the analysis of pathway-based SNP-SNP interactions. *Aging Cell*. 2018;17(3). doi:10.1111/acel.12755
16. Age-dependent expression changes of circadian system-related genes reveal a potentially conserved link to aging.
17. Rangaraju S, Levey DF, Nho K, et al. Mood, stress and longevity: Convergence on ANK3. *Mol Psychiatry*. 2016;21(8):1037-1049. doi:10.1038/mp.2016.65
18. Longo VD, Di Tano M, Mattson MP, Guidi N. Intermittent and periodic fasting, longevity and disease. *Nat Aging*. 2021;1(1):47-59. doi:10.1038/s43587-020-00013-3