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Probing the Genetics Impacts on the Process of Human Longevity

Mudather Elnoor Younis,Mustafa Abakar Mustafa

Faculty of Medical Laboratory Science -EL-Daein University

mudtherelnoor@yahoo.com

Abstract : *The objective of the current study was to investigate how genetics influence the process of human aging, from birth to death, human aging is a continual process that involves changes in one's physical, social, psychological, and spiritual aspects. Even though aging is a continuous process, its value is viewed differently depending on where it is in the process. Certain developments, like a baby's first tooth or walk, are eagerly awaited. According to evolutionary theories, there are genes that confer a selection advantage early in life and have a negative impact on lifespan later in life (antagonistic pleiotropy theory). These genes are also known as longevity insurance genes (disposable soma theory). In almost all creatures, aging is a process that seems inevitable and results in a decline in function. Lately, cellular senescence has come to be recognized as a primary cause of aging as well as a characteristic of aging.*

Introduction

From birth to death, human aging is a continual process that involves changes in one's physical, social, psychological, and spiritual aspects. Even though aging is a continuous process, its value is viewed differently depending on where it is in the process. Certain developments, like a baby's first tooth or walk, are eagerly awaited. Reactions to some changes are less enthusiastic, like plucking out the first gray hairs to show. Human civilization values youth, thus wrinkle treatments, facelifts, and hair colors are used to cover up age signals. When the youthful attractiveness starts to alter, the process of physical growth, which is so highly desired in the early stages of life, is seen extremely adversely. [1] Socially in both "developing" and "developed" countries. The U.S. Census Bureau's 2002 Global Population Profile indicated that there were 6.2 billion people on the planet. Out of this, roughly 7% of the population might be considered elderly, or 65 years of age and older. Varied societies and cultures have varied definitions of old age. It's a relative concept, with varying interpretations given in various situationsHandler gave an even more precise definition of aging: "Aging is the deterioration of a mature organism resulting from time-dependent, essentially irreversible changes intrinsic to all members of a species, such that, with the passage of time, they become increasingly unable to cope with the stresses of the environment, thereby increasing the probability of death" (Handler, 1960, p. 200). Aging is the term used to describe the normal changes that occur as a mature, genetically representative organism ages and lives in a representative environment. [2] Only recently has the genetic analysis of life duration in mammals, yeast, and invertebrates like Caenorhabditis elegans and Drosophila began. It is physiologically observed that life duration and metabolism rate are closely related, even at this early stage of the genetic research of aging. Numerous organisms, including mice, worms, flies, and yeast, have altered metabolism due to genetic variations that impact life duration. In C. elegans, insulin signaling controls life span in concert with metabolism, reproduction, and the control of genes that defend against free radical damage. Neuroendocrine cells in a variety of animals may be influenced by genes that dictate lifespan. The involvement of insulin-like hormones raises the possibility that variations in the timing of the release of the hormones that regulate vitality and mortality, as well as variations in the response to those hormones, are responsible for the flexibility in life lengths seen in animal phylogeny. [3] Human life expectancy has increased at an extraordinary rate during the last 200 years. It will be necessary to comprehend the underlying mechanisms of aging in order to sustain longer lives with fewer periods of incapacity, and genetics is a useful tool for figuring out these mechanisms. Recent large-scale genome-wide association studies have pinpointed numerous loci influencing important aspects of human aging, such as lifespan. Numerous age-related disorders have been linked to multi-trait loci, showing that ageing processes are common. The usual progeria syndromes in humans are caused by mutations that accelerate aging, suggesting a crucial role for genome stability and maintenance. When combined, these several lines of genetic study are pointing to potential avenues for human application-specific anti-aging therapies.[4] Ageing is a natural part of life, just like childhood, adolescence, and infancy do. It starts as soon as adulthood is attained. The main focus of gerontology, or the study of aging, is on the changes that take place in an individual between the time they reach adulthood and pass away. The aim of gerontological research is to determine the variables influencing these alterations. By using this understanding, some problems that are frequently linked to aging can be less severe. The goal of the current study was to investigate how genetics affects the process of human longevity [5].

Physiological aspect of aging

The rate at which each body system ages varies from person to person, for example, the heart, liver, metabolic system, and immune system. The human body has its own aging mechanisms. (6) Elderly people experience a variety of behavioral changes as they age, one of which is a change in eating habits. These changes may or may not be brought on by medical advice. Other factors that may

contribute to these behavioral changes include age-related taste changes, decreased saliva, and less appetizing food [7]. The physiological changes associated with aging that affect the elderly can be classified into four basic systems: sensory, neuro-endocrine, cardio-pulmonary, and musculoskeletal [8]. The amount of red blood cells in elderly people is within the normal range, but as they age, their resistance to mechanical shock increases and their diameter grows greater than in young people [9]. The skin's epidermis thins and collagen fibers thicken during the typical aging process. A greater propensity for skin breakdown as a result of pressure and ripping exists, and aging has an impact on the musculoskeletal system by reducing range of motion, increasing discomfort, and raising the risk of contracture. [10] Even in the absence of illness, the effects of aging on the lungs cause pulmonary physiologic performance to be compromised. As one ages, the lung gradually deteriorates, leading to increasing changes in elasticity, diminished mucociliary clearance, dilated air gaps, and loss of alveolar surface area.[11] Conversely, aging affects the cardiovascular system by increasing left ventricular stiffness and decreasing compliance: reduced diastolic filling and relaxation of the left ventricle, increased stroke volume, decreased maximal cardiac output, and decreased vasodilator response to exercise. Aging also has an impact on the neurological system. Decrease in complex visuoconstructive and logical analysis skills; decrease in processing speed, reaction time, and ability to shift cognitive sets rapidly; decline in executive function and memory distraction; abnormal reflexes; shrinkage of the hippocampus and frontal and temporal lobes; decrease in the number of receptors of all types in the brain with increased sensitivity. [12] Numerous alterations are brought about by physiological aging in the brain, including reductions in cortical thickness, increases in white matter hyperintensities, and decreases in both grey and white matter volume. It alters how the brain functions, which results in a decrease in processing speed, executive function, and the capacity to recall recently taught material. Heightened risk of neurodegenerative illness and cognitive impairment. Alzheimer's is an age-related disease. Additionally, genes (GABRA3, CYFIP2) that are implicated in physiological aging may vary with age. [13]. Aging can cause microscopic alterations in the kidneys, including fibrosis, atrophy in the quantity and quality of tubules, scarring of the glomeruli that filter urine, and thickening of the arterial walls.Macroscopic alterations include decreased bulk, weight, and length; more cysts and calcification; and an aging-related decrease in renal parenchyma capacity.Both the macroscopic and microscopic causes result in functional changes (reductions in renal blood flow, glomerular filtration rate, sodium resorption, tubule transport, and the capacity to concentrate or dilute urine, as well as a decline in acidification and an impact on renin synthesis).Functional alterations lead to clinical changes, such as greater vulnerability to acute renal injury and the advancement of chronic kidney disorders. [14] According to recent research, aging affects the lung in the following ways:progressive loss of alveolar surface area, dilating air gaps, decreased mucociliary clearance, elasticity changes, quantitative and qualitative deficiencies in the cells that make up the airway, and aging-related alterations in the various lung cells; reduction in the amount of basal cells, decreased differentiation and self-renewal, and increased apoptosis of club cells and ciliated cells (lower ciliary beat frequency and fewer ciliated cells)Age-related GLEI/ARSMG manifestation in glandular-like epithelial invaginations Impaired differentiation into AT1 cells, senescence, endoplasmic reticulum stress, an increase in MHC class I genes, altered lipid metabolism, and increased cholesterol production are among the alterations in alveolar type 2 cells Alveolar type 1 cells are altered by a consistent expansion of airspace and a decrease in AT1.Male characteristics include enlarged prostate, elevated prostate-specific antigen, dry vagina, thinning vaginal mucosa, and asymptomatic bacteruria phenomena.[11,9] Aging is said to produce numerous structural and functional changes in the cardiovascular system; Myocyte loss accompanied by a gradual increase in the volume of each nucleus of the surviving myocytes and hypertrophy of the remaining myocytes gradual loss of pacemaker cells in the sinus node, thickening of the wall, and diastolic dysfunction, all of which are risk factors diastolic heart failure, elevated systolic and pulse pressures, elevated systemic vascular resistance, endothelial dysfunction—a risk factor for atherosclerotic disease—and arterial sclerosis Reduced cardiopulmonary reflex and delayed arterial baroreceptor reflex response cause electrolytic imbalances, disrupt bodily fluid homeostasis, disrupt microcirculation, and lower maximal heart rate, maximal cardiac output, and maximal oxygen consumption.[15] There are two primary categories into which the immune system's aging changes can be divided: First, as people age, their innate immune systems are affected by changes in anatomical barriers, a decrease in Langerhan cells,Impact on DCs' ability to recognize pathogens because of the presence of fewer functional NK cells; decreased neutrophil survival in response to stimuli; decreased neutrophil phagocytic function and respiratory burst generation; decreased macrophage production of cytokines; and decreased macrophage activation of T cells. The second way that aging affects the adaptive immune system is through a decrease in the production of lymphoid progenitors, a decrease in the number of B cells, an increase in the memory B cells' resistance to apoptosis, a decrease in the production of antibodies with fewer affinities and opsonizing abilities, a delay in the antibody response to novel antigens, and a decrease in the number of T cells, particularly naive and CD8+ cells.Increase naive T cell activation and proliferation without the need for antigen, and reduce CD28+ T cell count due to the accumulation of mature lymphocytes**,** age also affects cytokines, which increase memory T cells' resilience to apoptosis, increase T cells' acquisition of NK cell markers, and decrease CD8+ cells' capacity for cytotoxicity.TNF-a, IL-6, and IL-1 are elevated, Increased disruption of cytokine production, elevated IL-2, elevated IL-8, decreased interferon-g, and modified NK cell cytokine responsivenessAntigen processing cells upregulate IL-10 and IL-12 because elderly individuals' immune systems have changed, making them more susceptible to infections, having weakened immune responses to vaccinations, and having inferior reactions to both recognized and novel antigens. Chronic low-grade inflammation, which is more common among the elderly. Moreover, the prevalence of cancer is rising. [15].

Genetics and aging

In order to find the genes responsible for aging and longevity, known as gerontogenes, model organisms are usually used to search for mutant strains whose rate of aging deviates noticeably from that of a control group. The following are the two most effective ways to find novel genes: (1) Gain of function: longevity rises in a mutant with an overexpressed candidate gene; (2) Loss of function: lifespan increases when the gene is inactivated. [16] Examples of genetic variations linked to aging include polymorphisms at the PON1, IGF1 receptor, PI3K, and APOC3 genes. Additionally, a sizable portion of the genome is associated with genetic variations connected to age-related illnesses. Examples include functional SNPs in CD244 linked to rheumatoid arthritis and type 2 diabetes, and genetic variations in APOE and PCDH11X linked to Alzheimer's disease. [17]. Many aging phenotypes in humans are accelerated by a few heritable mutations. These mutation-caused disorders are referred to as segmental progeroid syndromes because they accelerate some but not all of the normal aging symptoms. RecQ-like DNA helicase genes were mutated to cause the human Bloom, Werner, and Rothmund-Thomson syndromes. Of these three syndromes, Werner syndrome (WS) is the finest illustration of premature human aging due to its adult onset and remarkable similarities to normal aging. [18] By modifying the availability of the monomethyl and dimethyl substrates for the trimethylation enzymes, the NSD1 gene catalyzes the addition of monomethyl (H3K36me) or dimethyl groups (H3K36me2) and regulates the amounts of trimethylation (H3K36me3). Therefore, a phenotype that can include prenatal and postnatal overgrowth, facial gestalt, advanced bone age, developmental delay, higher cancer propensity, and, in certain cases, heart problems, results from this gene losing function owing to mutation. Numerous of these traits are suggestive of aging, suggesting that Sotos disease may be a human model of accelerated physiological aging. [19] Additionally, deletion mutations in the genes homologs of phospholipid hydroperoxide glutathione peroxidase (PHGPx) can accelerate aging and cause Caenorhabditis elegans to have shorter lives. [20] The genetic theory of aging postulates that our genes play a major role in determining how long we live. The hypothesis holds that our longevity is mostly influenced by our parents' DNA and is decided at the time of conception. [21]This notion is based on the idea that telomeres—short DNA segments found at the ends of chromosomes—determine a cell's maximum lifespan. Every time a cell divides, the ends of chromosomes, known as telomeres, contain shorter segments of "junk" DNA. These telomeres eventually get shorter and shorter, making it impossible for the cells to proliferate without losing critical DNA fragments.[22] Aging is a pathological process that combines our understanding of age-related chronic diseases, functional loss, and frailty. One significant aspect of aging is inflammation [24]. The innate and acquired immune systems undergo remodeling as we age, and as a result, the immune system becomes less dependable and effective. This can result in an increase in the inflammatory response and the development of associated degenerative diseases. [23]

Discussion

The field of genetics of aging primarily studies life extension linked to genetic modifications, as opposed to accelerated aging disorders that shorten life spans.The age-1 gene in Caenorhabditis elegans was the first mutation to be discovered to lengthen an animal's lifespan. While Michael Klass found that mutations might change the lifetime of C. elegans, Klass thought that the impact was caused by calorie restriction. [24]

Later research by Thomas Johnson demonstrated that the mutation itself, not calorie restriction, was responsible for the up to 65% life extension. In [25] Researchers at Northwestern University have uncovered a yet unidentified process that propels aging.In a recent study, scientists analyzed data from a wide range of tissues, including those from humans, mice, rats, and killifish, using artificial intelligence. They found that most aging-related alterations at the molecular level may be explained by the length of genes.Long and short gene activity must be balanced in every cell. The researchers discovered that lifespans are correlated with longer genes and shorter genes with longer lifespans. It was also shown that the activity of aging genes varies with length. More precisely, a change in activity toward short genes is associated with aging. This throws off the balance of gene activity in the cells. [26] Developing targeted anti-aging medicines requires an understanding of the genetic and epigenetic aspects of aging. However, what we know about the genetics and epigenetics of aging is still very limited. The aging process is dynamic and complicated, therefore real-time, dynamic, multi-dimensional monitoring of the aging process can be achieved through increased use of genomics and epitranscriptomics technologies.Comprehending the intricate genetic and epigenetic processes of aging will facilitate the detection of aging-associated indicators, potentially leading to the creation of efficacious remedies against this progression. [27] Enhancing longevity is the primary goal of research on anti-aging. At the moment, novel gene therapy-based strategies appear to be among the most promising for treating and preventing age-related and other chronic polygenic illnesses. Gene-based therapy makes it possible to modify the genome's architecture using both direct and indirect means, such as gene editing and viral or non-viral vectors. However, the efficacy of these treatment choices is frequently insufficient and constrained by their side effects, given the incredibly intricate mechanisms involved in aging and age-related disorders. As a result, putting such applications into practice clinically will undoubtedly take time and involve multiple translation stages to overcome obstacles. Nevertheless, once these problems are resolved, their application in clinical settings may undoubtedly open up new avenues for anti-aging research. Here, we examine and talk about the most recent developments in this quickly advancing field of study. [28] Numerous age-related disorders have been linked to multi-trait loci, showing that ageing processes are common. Human progeria syndromes that are typified by mutations that cause accelerated aging suggest that genome stability and maintenance play a significant role. When combined, these

several lines of genetic study are pointing to potential avenues for human application-specific anti-aging therapies. [29] A genome-wide CRISPR-Cas9 screen was carried out by Wang et al. in order to find genes that might have an impact on cellular senescence.They discovered that KAT7 causes senescence in adult human stem cells. KAT7 inactivation regenerated progeroid human cells that were aging too quickly and increased the longevity of mice.Although it is known that cellular senescence, a permanent growth halt condition, accelerates aging, it is yet unknown how this process works. Our comprehension of the mechanisms behind cellular senescence is crucial for creating anti-aging and longevity-promoting therapies. [30] Even while we're learning more about what happens to the human body as it ages, the majority of the knowledge we possess about the genes involved in aging comes from studies conducted on short-lived model species like fish, worms, yeast, and flies. Investigating the impact of genetics on the development of human longevity is therefore still a crucial objective.

Conclusion

In almost all creatures, aging is a process that seems inevitable and results in a decline in function. Lately, cellular senescence has come to be recognized as a primary cause of aging as well as a characteristic of aging. Over time, senescent cells build up in tissues, causing organismal aging's inherent characteristics and exacerbating age-related illnesses like Alzheimer's and arthritis. The development of anti-aging therapies will be facilitated by the discovery of new age-related genes; further research is required to comprehend the mechanisms underlying the genetic and epigenetic factors linked to aging.

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