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Review

Aging Genetics and Aging

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ABSTRACT: The process of aging refers to the decay of an organism's structure and function, in which molecular and cellular modifications can have various effects at the individual level over the course of a lifetime. The accumulation of molecular errors that compromise adult stem cell functions occurs because of genetic and epigenetic interactions and depends on hereditary, environmental, and stochastic factors. Here we review the known genetic factors involved in aging.

***Key words*:** Longevity; Environment; Genes; Progerias; DNA repair and telomeres

Aging affects physiological functions and can be defined as the accumulation of damage in molecules, cells and tissues over a lifetime; this often decreases an organism's capacity to maintain homeostasis in stress conditions, and entails a greater risk for many diseases (cancer, cardiovascular and neurodegenerative disorders) and premature mortality[1, 2]. Identification of factors that regulate aging is limited by the complexity of the process and by the considerable heterogeneity among individuals and even among tissues within a body. At the cellular level, the most prominent event in an aging tissue is cell senescence, a consequence of exposure to intrinsic and extrinsic aging factors; it is characterized by gradual accumulation of DNA damage and epigenetic changes in DNA structure that affect correct gene expression and lead to altered cell function.

Aging is a multifactorial process that is determined by genetic and environmental factors. The genotype determines the variation in lifespan among species or individuals; this variation is more severely affected by the tendency to accumulate molecular errors that compromise adult stem cell function than by a specific genetic program[3]. Here, we review the best known genetic factors involved in aging.

Cell aging: DNA damage and telomeres

A principal factor in aging is an exponential increase in incidence and mortality rates of cancer and non-cancerous diseases, as well progressive tissue degeneration and atrophy, caused by a decrease in adult or somatic stem cell function [4].

Cells are constantly exposed to a harmful environment throughout life. Increasing cell damage contributes to the dysfunction that characterizes the aging body. The best example of DNA damage as a cause of aging are the progeroid syndromes, which are caused by a deficiency in the mechanisms involved in DNA repair and whose symptoms begin early in life[5, 6].

Mutations in certain genes confer greater stress resistance and a reduced rate of damage accumulation, increasing longevity. For example, mutation in the gene that encodes the oxidative stress response protein $p66^{shc}$, which prolongs life and protects from a variety of aging-

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associated diseases in mice, enhances resistance to apoptosis following oxidative stress *in vitro*-cultured cells [7].

Telomeres are DNA-protein complexes that cap the ends of linear DNA strands, stabilizing them and preventing chromosome instability [8]. A correlation has been proposed between telomere shortening and somatic stem cell decline during aging [9]. The enzyme telomerase adds specific DNA sequence repeats to the chromosome ends that are lost through cell division, thus restoring telomere length and delaying cell senescence, apoptosis, and death [10]. The repetitive DNA at chromosome ends shortens with age, as observed in fibroblasts, lymphocytes, and hematopoietic stem cells (HSC) [11]. Telomeres become critically short after repeated mitotic divisions without adequate telomerase activity, making cells susceptible to apoptosis, death and to a clear increase in mutation [12, 13].

Telomere shortening is associated with age-related diseases in humans [14], and patients with accelerated aging syndromes show a higher rate of telomere erosion and marked chromosome instability[9]. Consistent with this, telomere dynamics are important for HSC maintenance [15], telomere shortening impairs adult stem cell function [16-18], and telomerase-deficient mice have short telomeres and age prematurely [9]; most strikingly, telomerase-overexpressing mice have longer telomeres and show delayed aging and cancer resistance [19]. The pathways that involve DNA sequence alterations in somatic stem cell aging are still unclear, but these findings raise the possibility that telomere length or deficiencies in DNA repair systems could be part of these routes.

Genetic factors in aging

Several genetic factors are implicated in aging. Specific gene combinations (genotypes) determine lifespan: remarkable changes in duration are observed as a result of alteration in a single gene, as in human progeroid syndromes [20]. Twin studies show the impact of hereditary factors in lifespan variation [21, 22], which concur with the wide range of genetic variants involved in aging and age-related diseases described in genome association studies in centenarians[23]. In addition, mutations in genomic and mitochondrial DNA are a consequence of reduced repair efficiency, and lead in part to deterioration of somatic stem cell function [4].

Examples of the importance of genetic factors in aging include genes that maintain organism structure and function throughout life, alleles that enhance reproductive capacity early in life but have negative effects later in life when their impact has escaped natural selective pressure, and constitutional mutations that are phenotypically relevant until late in life, when they have eluded selection and cannot be removed from the population [24-26] .

Two main classes have been described of lifespan-extension mutants in *Caenorhabditis elegans*. The first consists of genes with activity in the mitochondrial electron transport chain, such as *clk-1* [27] and *isp-1* [28], whose mutation moderately reduces oxidative phosphorylation capacity and prolongs life in worms [29]; these mutations established the first link between energy metabolism and longevity. The second mutant class is related to hormone mechanisms of the insulin/IGF-I signaling (IIS) pathway, such as *daf-2* and *age-1* mutants [30, 31], which extend lifespan in worms, flies and mice [32].

The *clk-1* mutant lacks an enzyme implicated in the biosynthesis of ubiquinone (coenzyme Q), an electron acceptor in the respiratory electron transport chain. Mice with moderately reduced oxidative phosphorylation have improved glucose homeostasis and live longer [33, 34]. Mutation of *isp-1*, which encodes an iron sulfur protein in mitochondrial complex III, was the first evidence of lifespan extension caused by an impaired electron transport function [35-37]. These findings suggest that reduced mitochondrial function could promote aging.

IIS is mediated by DAF-2, the insulin/IGF-I receptor. *C. elegans daf-2* mutants with reduced DAF-2 activity remain young and live longer than wild-type worms [31]. The life-prolonging effect of the *daf-2* mutant is suppressed by mutations in *daf-16*, which is negatively regulated by DAF-2 signaling. *daf-16* encodes a FOXO transcription factor [38] that regulates genes involved in defensive activities such as cell stress response, antimicrobial activity, detoxification of xenobiotics and free radicals.

Suppression of the TOR pathway, which interacts with IIS, lengthens *C. elegans* lifetime [39]; following TOR activation, the insulin receptor signaling pathway downregulates expression of proteins in the sirtuin family and inhibits autophagic mechanisms involved in cell integrity, through removal of damaged mitochondria. Both pathways are essential for lifespan extension, as shown by longevity mutants of *C. elegans* [40-42].

Sirtuins are protein deacetylases that modulate pathways implicated in the aging process [43]. Certain sirtuins regulate glucose and fat metabolism in mammals [44, 45] by enhancing mitochondrial biogenesis in liver and muscle through the transcriptional coactivator peroxisome proliferator-activator receptor-γ coactivator 1α (PGC-1α) [45]; they also govern cell survival by reducing p53 tumor suppressor activity [46, 47].

Resveratrol, a plant-derived polyphenol, increases the deacetylase activity of some sirtuins and increases yeast lifespan by nearly 70% [48]. Similarly, when treated with resveratrol, the short-lived fish *Nothobranchius furzeri* also showed a 60% increase in lifetime, accompanied by maintenance of motor and cognitive capacities [49]; resveratrol-treated middle-aged mice on a high-calorie diet showed a significant lifespan extension [50].

Specific genetic factors that determine length of life

Current understanding of biological aging implies that some aging-associated changes are programmed, whereas others are random and not predictable. Human senescence is a complex process involving genetic and environmental factors that affect most physiological pathways. The enormous variation in the average lifespan in different species suggests that maximum lifetime is determined by the species-specific genotype (**Fig. 1**). Identification of genes and mutations responsible for progeroid syndromes (age-related monogenic hereditary disorders) [20] will help to establish the function of a specific genotype in an individual's lifespan.

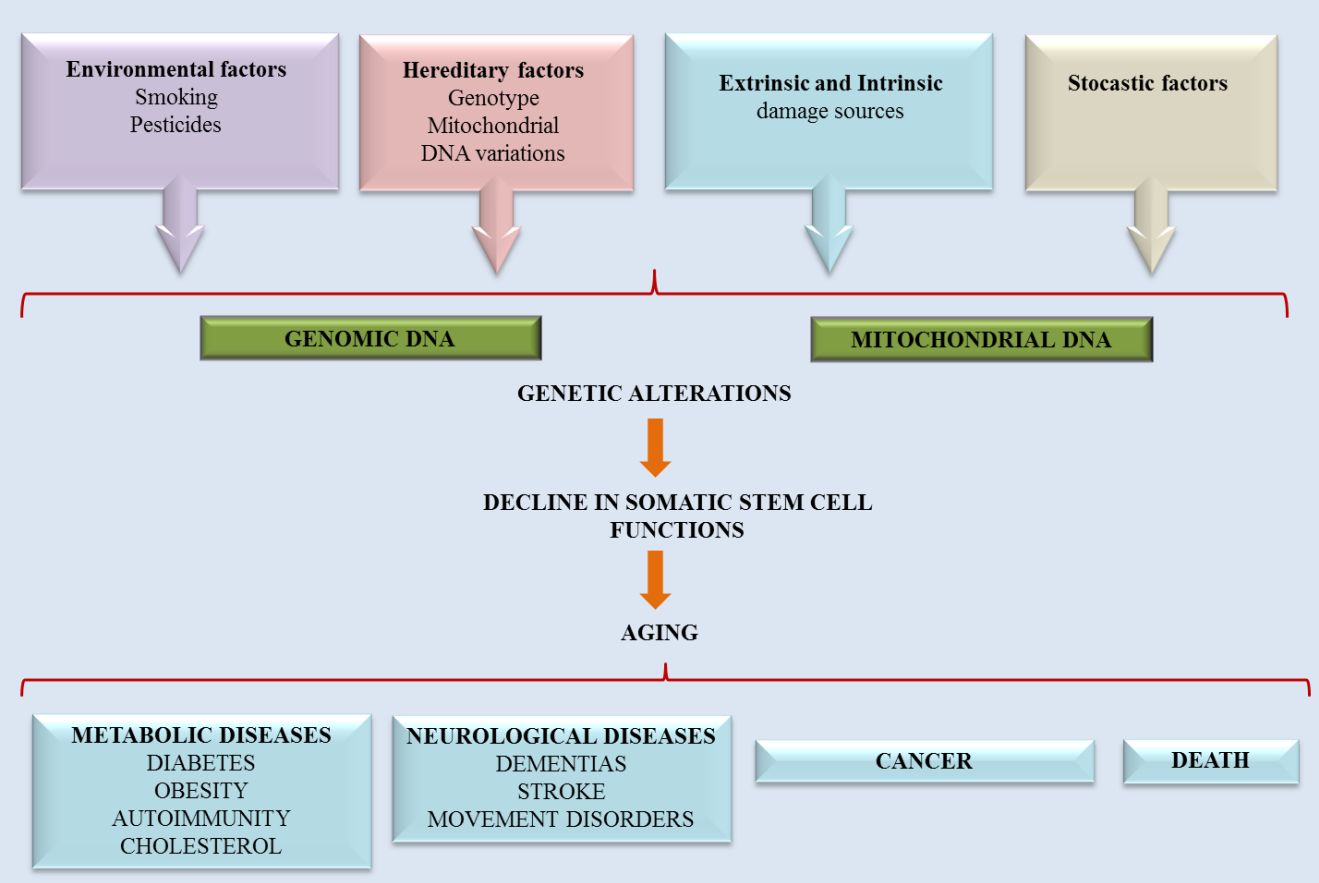

Figure 1. Representation of genetic factors´ influence in aging and lifespan. The environmental conditions (stress, pesticides), individual genotype (genomic and mitochondrial DNA) and stochastic factors can induce genetic and epigenetic alterations that cause a decline in somatic stem cell function that can be the origin of metabolic, degenerative diseases, cancer and aging in the individuals.

Progerias are a group of diseases characterized by a premature aging phenotype and are a model for studying aging-associated genetic changes. Patients with these conditions, including Cockayne syndrome, Fanconi anemia, Werner, Bloom, Rothmund-Thomson and Hutchinson-Gilford syndromes, xeroderma pigmentosum and ataxia-telangiectasia, develop features of accelerated aging caused by mutations in genes implicated in genetic stability (**Tabe 1**). The clinical characteristics of progerias can include premature senescence (gray hair, atherosclerosis, increased risk of cancer), skin changes (atrophy, ulcer, hyperkeratosis), metabolic disorders (diabetes, hyperlipidemia) and senile dementia. Also termed "segmental progerias", these syndromes are often selective of certain features of physiological aging.

Werner syndrome (WS) is an autosomal recessive progeroid syndrome caused by mutation at *WRN*, a member of the RecQ helicase family [51], involved in DNA repair systems and replication [52-54]. WS patients develop normally until puberty; the first sign of disease is absence of the pubertal growth spurt and gonadal atrophy, which results in short stature of the affected adult. By the third decade of life, premature graying, loss of hair and skin atrophy become apparent; they also show accelerated development of all forms of arteriosclerosis, type 2 diabetes mellitus, regional loss of subcutaneous tissue, osteoporosis, ocular cataracts, and increased cancer susceptibility [55, 56]. Individuals with WS show reduced telomere length in fibroblasts, which cease to divide prematurely, as well as deficiency in DNA repair systems, leading to genomic mutations that increase cancer incidence [56-61].

The Hutchinson-Gilford progeria syndrome (HGPS) is a rare autosomal dominant genetic disease. As for other segmental aging syndromes, its clinical signs include precocious aging in early childhood with reduced life expectancy; patients do not usually reach adolescence [62]. This syndrome is a laminopathia caused by a single-base substitution (GGC>GGT) at position 1824 in exon 11 of the *LMNA* gene [63, 64]. *LMNA* encodes the nuclear lamin A protein, a constituent of the nuclear lamina, a structure that has an important role in nuclear stability [65, 66]. Truncated lamins caused nuclear anomalies compatible with the HGPS phenotype [67-73]. Several animal models of progerias have confirmed the effect of a single genetic alteration on the mechanisms of aging. Mice with a mutation in the LMNA gene or deletion of the metalloprotease that processes prelamin A (Zmpste24) acquire a pathologic phenotype similar to HGPS syndrome [74, 75].

Bloom syndrome is a rare hereditary disease characterized by short stature, telangiectasia (tiny blood vessels dilated facial) facial photosensitivity (increased sensitivity to light), and increased susceptibility to tumors. Bloom syndrome is a rare disorder in most populations. It is more common in people of Central and Eastern European (Ashkenazi) Jewish background, among who 1 in 48,000 are affected. This syndrome is associated with mutations in the BLM gene, which encodes a protein family of DNA helicases (enzymes involved in DNA replication and transcription) [76]. These individuals have chromosomal instability by a high frequency of breaks and rearrangements with abnormal sister chromatid exchanges, increased sensitivity to ultraviolet radiation and alterations in DNA synthesis. Alterations have also been located on chromosome 15q26. The higher frequency in Ashkenazi Jewish population s is due to a founder effect; approximately 1% of them are heterozygous carriers of the LMAsh mutation (a six nucleotide deletion and a seven nucleotide insertion at position 2281 of the cDNA) [77].

Rothmund-Thomson syndrome (RTS) is inherited as an autosomal recessive disease and presenting early in life with clinical characteristics such as facial rash (poikiloderma), short stature, sparse scalp hair, sparse or absent eyelashes and/or eyebrows, juvenile cataracts, skeletal abnormalities, premature aging and a predisposition to osteosarcoma [78]. This spectrum of clinical features is suggestive of genetic heterogeneity. It has been described in all ethnic groups with a very low prevalence.

Two subtypes of this disease have been found in the affected individuals, the type I RTS is characterised by poikiloderma and juvenile cataracts is negative for the RECQL4 mutation [78], while the type II RTS, is characterised by poikiloderma, congenital bone defects and an increased risk of osteosarcoma in childhood and skin cancer later in life, is caused by homozygous or compound heterozygous mutations in the RECQ4 helicase gene [78].

Progerias are excellent examples of the influence of genetic factors on the aging process, and understanding the mechanisms involved in these pathologies will contribute to the development of new treatments for these patients.

Linkage and association studies of genetic variants that affect longevity and aging

The observation that certain genetic factors act as modulators of the aging process has led to the development of studies in populations of centenarians, whose lifespan is approximately twice the mean predicted for the population at the time of their birth [21, 22]. The longevity of these individuals is often

accompanied by increased resistance to diseases that lead to early death [79, 80]. In families whose members show exceptional longevity, in addition to other environmental factors, family habits (lifestyle, nutrition) were thought to influence survival, although data are limited on the contribution of these factors to greater resistance to disease [81].

Table 1. Genetic alterations associated to premature aging phenotypes

Syndrome	Gene	Function
Cockayne Syndrome	ERCC6(CSA) ERCC8 (CSB)	DNA repair
Fanconi Anemia	FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM FANCN	DNA repair
Werner Syndrome (WS)	WRN	DNA helicase
Bloom Syndrome	BLM	DNA helicase
Rothmund- Thomson Syndrome	RECQL4	DNA helicase
Hutchinson- Gilford Syndrome	LMNA	Structural Protein

Aging-associated polymorphisms in the *IGF1R*, *PON1*, *APOC3 and PI3K* genes [82] and the evolutionarily conserved extension in longevity through IIS[83, 84] are examples of the genetic factors involved in extreme longevity. The IIS equivalent in mammals is part of the somatotropic axis that regulates body growth. Somatic growth is mediated by growth hormone (GH), which is released by the hypophysis. Circulating GH activates the GH receptor (GHR); this in turn leads to secretion of IGF-1, which binds the IGF-1 receptor (IGF-1R) on target cells, triggering cell growth and survival [85]. The role of GH in aging became clear in *Ghr* knockout mice, which showed increased longevity [86-88]. Specific polymorphisms associated with a decrease in plasma IGF-1 concentrations are frequently found in Ashkenazi Jewish centenarians [60, 89, 90], suggesting a role for GH and IGF-1 signaling downregulation in human longevity.

Willcox *et al*. [91] recently described three SNP (single nucleotide polymorphisms) in the *FOXO3A* gene, a homologue of the key IIS effector *daf-16* in *C. elegans*, that were significantly associated with longevity and aging phenotypes in a population of long-lived Americans of Japanese ancestry; these associations were confirmed by Flaschbart *et al*. [92].

A large number of genome-wide case-control association studies have identified many genetic variants linked to age-related diseases. Examples include the genetic variation in *APOE* and *PCDH11X*, associated with Alzheimer's disease (AD) [93, 94]. Individuals homozygous for the *APOE* ε2 allele have a longer lifespan than ε3 or ε4 carriers in Caucasian populations [95, 96], which could be linked to increased risk of coronary disease for these latter alleles [97]. Moreover, the ε4 allele appears to be associated with risk of developing the familiar and sporadic forms of AD, and ε4 carriers showed symptoms of the disease at younger ages [97, 98].

An adequate immune response seems to be related to increased lifespan; the alleles *HLA-DR11* and haplotypes HLA-B8, DR3 have a protective effect in infections and are associated with longer life; studies in Sicilian male centenarians show an increase in the presence of the HLA DRB1*18 allele in these individuals [99].

Singh *et al*. [100] described the association with extended survival of three single nucleotide

polymorphisms, *HSPA1A* (-110A>C), *HSPA1B* (1267A>G) and *HSPA1L* (2437T>C) of the three HSP70 genes. These authors found that HSPA1A-AA and HSPA1B-AA genotypes in a cohort Danish nonagenarian were significantly associated with poor survival in women and the female carriers of haplotype G-C-T survived longer than non-carriers.

Reactive oxygen species (ROS) are widely linked to aging, as part of the DNA damage mechanisms. Mutations in proteins that participate in free radical detoxification can also affect variation in aging and life span; the rs4880 and rs1050450 SNP in the *MnSOD* (manganese superoxide dismutase) and *GPX1* (glutathione peroxidase 1) genes, respectively, are associated with age-related diseases [101]. Decreased mortality was also described in individuals bearing the MnSODrs4880C (MnSOD(CC/CT) or the GPX1rs 1050450T alleles (GPX1(TT/TC) in a nonagenarian Danish cohort [102].

Although analyses of these long-lived populations have allowed the identification of loci that could be associated with a better chance of living longer, additional studies are needed to confirm these associations.

Concluding remarks

Aging is a complex process that can be described as a group of cellular functions that participate in an integrated way in the process of senescence. The great variability in longevity between individuals of the same species suggests that the aging process is profoundly affected by processes that lead to the accumulation of errors that damage repair systems and compromise stem cell function. These changes can be caused through genetic and epigenetic mechanisms, which are influenced by genes, environmental and stochastic factors; the contribution of each of these factors remains to be determined by future studies.

Aging is characterized by a progressive decline in physical, mental, and reproductive capacity, as well as an increase in morbidity and mortality. Damage invariably accumulates with age and contributes to the cell dysfunction that characterizes this process, and is clearly influenced by genetic and environmental factors. The effects of the variety of factors involved in aging are the result of the balance between our defense and damage repair systems and the aggression to which we are subjected [103]. Defense and repair systems are highly enzyme dependent; the absence or malfunction of a gene necessary for production and activity of these enzymes can lead to accumulation of cell damage, as demonstrated by the progeria syndromes.

There is increasing evidence that, in addition to genetic factors, age-associated alteration of gene function might also depend on epigenetic factors. Examples of epigenetic alterations with age include global DNA hypomethylation and promoter hypermetylation. Thus, aging is not probably mediated by a single gene or main mechanism. The magnitude of the contribution of the pathways cited above to the onset and progression of aging and age-related diseases remains unclear. Many questions regarding epigenetic and its role in age related diseases still remain open, but may be able to explain many of the phenotypic changes related to the aging process. Further studies are needed to describe the pathways involved in age-related physiological alteration (hypertension, insulin resistance) and predisposition to age-related pathological changes (cancer, neurodegenerative disease). Exploration of these functional connections might provide options to help develop more efficient anti-aging strategies to ameliorate senescence-related diseases. Exploration of these functional connections might provide options to help develop more efficient anti-aging strategies to ameliorate senescence-related diseases.

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