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Genetic and Environmental Contributions to Human Longevity

Genetik ve Çevrenin İnsan Ömrüne Katkıları

Awoyemi Abayomi Awofalal[1,2], Olesegun Emmanuel Ogundele[2]

[1] Cyprus University of Technology, Limassol, Cyprus
[2]Department of Biological Sciences, Tai Solarin University of Education, Ijagun, Ogun State, Nigeria

ABSTRACT

Human longevity, like most complex phenotypes, is thought to reflect a complex interplay of both environmental (e.g. lifestyle choices, where we live in) and genetic factors. These factors are likely to influence the basic mechanism of ageing and in turn broadly influence susceptibility to age-related illness. Thus, good lifestyle choices and conducive environment coupled with lack of genetic variants that predispose to diseases as well as having variants that confer resistance to diseases are probably vital to achieving old age. Although, the scientific understanding of the mechanism governing longevity is still sparse, understanding its biological underpinnings, including the potential contribution of genes and environment, is a key for shaping individual's lifestyle choices and developing efficacious therapeutic targets to increase lifespan. This review provides an overview of different strategies that are being integrated increasingly to extend our knowledge of the genetic and environmental underpinnings of human longevity.

Keywords: Human longevity, genes, environment, epigenetics, gene-environment interaction.

ÖZET

İnsan ömrünün en kompleks fenotipler gibi, hem çevresel (yaşam tarzı, nerede yaşadığın gibi) hem de genetik faktörlerin kompleks etkileşimlerinin yansıması olduğunu düşündürür. Bu faktörler muhtemelen yaşlanmanın temel mekanizmalarını ve büyük ölçüde yaşla ilişkili hastalıkları etkiler. Hastalıklara direnç gösteren varyantların eksikliği kadar hastalıklara yatkınlığı arttıran varyantların varlığında da iyi yaşam tercihi ve tamamlayıcı çevre varlığı ileri yaşlara ulaşmada hayati önem taşıyacaktır. Uzun yaşamın bilimsel mekanizması hakkındaki bilgilerimiz hala yetersiz olmasına rağmen, çevrenin ve genlerin potansiyel katkıları da dahil yaşlanmanın biyolojik temellerini anlamak bireyin yaşam tarzı tercihlerini şekillendirmesi ve ömrünün uzaması için etkili tedavi hedefleri

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geliştirmek için anahtardır. Bu derleme, insan uzun ömrünün genetik ve çevresel temellerinin entegre edildiği farklı stratejilere farklı bir bakış açısı sağlayacaktır.
Anahtar kelimeler: insan ömrü, genler, çevre, epigenetik, gen-çevre etkileşimleri

Introduction

Surviving to old age is probably a multifactorial phenotype involving multiple biological processes, environmental influences and randomness[1, 2]. Extreme longevity commonly results not only from genetic and immune system advantages that reflect a minor risk for developing major age-related diseases such as cardiovascular diseases, hypertension or diabetes mellitus and cancer[3, 4] but also good environmental qualities reflecting the notion that agents who live longer have a stronger concern for the future and thus invest more in environmental care[5]. In recent years, there has been global increase in life expectancy over time albeit with persistent increase in variability between countries over the past half-century[6,7]. The gap in life expectancy between the more developed and the less developed countries for instance, is perhaps a reflection of their differences in accessibility to health facilities and environmental care[7]. Today, a considerable interest in understanding how individuals achieve a long and healthy life has grown, thus further depicting the importance and social implications of health and longevity.

Many probing questions including how long a human can live and why some individuals live longer than others emanated from the obvious differences in life expectancy and variations in lifespan among individuals of different populations. Alienating this variation is complex and multifaceted as a result of the genetic make-up of an individual and the environmental perturbations over time in the populations. Notably, designs from genetic epidemiology including family, twin and adoption studies centre on cohort, case-control and experimental studies have however, proved useful in assessing the relative contribution of genes and environment for this variation in longevity. Advances in this field have renewed interest in the genetic and environmental basis for human longevity.

Twin, Family and Adoption Studies

If there are certain genes that modulate ageing, and are heritable, it then follows that genetics does play a strong role in human longevity. To disentangle the shared roles of genes and environment on longevity, the twin and adoption studies are often used. The twin study design compares the similarities for longevity between monozygotic (MZ, identical by sharing

around 100% of their genes in common even though small differences may occur through mutation or changes in activity levels) twins and dizygotic (DZ, fraternal by having around 50% of their genes in common as will normal siblings) twins for evaluating the heritability of the condition. Adoption studies on the other hand, compare whether longevity in biological parents predicts longevity in children even when the child is reared by unrelated adoptive parents or vice versa. Interestingly, both studies have demonstrated a strong genetic component of premature death and with approximately 20-30% of overall variation in lifespan shown to be caused by genetic differences in a series of twin studies during the last decades[8-10]. A study based on data from the Swedish, Finish and Danish national twin registries for twins born between 1870 and 1910 made up of about 20,000 individuals followed until 2003-2004 has documented that having a co-twin surviving to old ages substantially and significantly increases the chance of reaching the same old age and this chance is higher for MZ than for DZ twins indicating evidence of familial clustering of longevity[1].

Genome-Wide Scans

Using non-parametric linkage analysis, Puca and co-workers in one of the first attempts at identifying genetics regions co-segregating with longevity phenotype, reported a region in chromosome 4 that could possibly harbor a gene affecting human longevity[11]. More recently, a large linkage analysis for longevity has been performed on 2118 nonagenarian Caucasian sibling pairs from the Genetics of Healthy Aging (GEHA) study. In this study, linkage with longevity was observed in four regions: chromosome 14q11.2 (logarithm (base 10) of odds (LOD=3.47), chromosome 17q12-22 (LOD=2.95), chromosome 19p13.3-13.11 (LOD=3.76), and chromosome 19q13.11-13.32 (LOD=3.57). Interestingly, the linkage in chromosome 19q13.11-13.32 explains the association of longevity with APOE $\varepsilon 4$ and APOE $\varepsilon 2$ alleles with *P-value* = 0.02 and *P-value* =1.03 x10^{-5}, respectively[12]. While linkage analyses are used to identify a broad chromosomal region that may likely contain a gene contributing to longevity, association studies on the other hand are carried out identify gene or genes contributing to longevity using a single marker analysis[13]. Association study in this case usually involves testing the association between a particular allele of the candidate gene and a specific phenotype (e.g. longevity). Such candidate gene is chosen either based on its suspected role in the phenotype or other known information relating to the outcome. In addition, gene could be chosen because it lies in a DNA region known to affect or linked to the disorder through linkage studies. Many candidate genes for longevity have been postulated. However, only a

few functional loci moderating this trait have been reported (see below). The genome wide scans have also been extended to take into account multi-locus association studies that take into consideration interactions among different genes[14].

This shift from single marker analysis [e.g. single nucleotide polymorphism (SNP)] for genetic association studies to haplotypes (involving different allelic configuration on an homolog) based analysis incorporate linkage disequilibrium information thus exhibiting more power[15]. Indeed, the development of haplotype mapping (HapMap) project[16,17] has led to the provision of a list of common haplotypes and haplotype blocks that are in linkage disequilibrium, thus enabling the haplotype-tagging SNPs for both population and family based studies[18]. It should however, be noted that any association study (be it family- or population-based) tests the null hypothesis that the frequency of a particular trait is the same in both patients and controls. Such studies have suffered from inadequate power due to small participant numbers, poor selection of control participants, confounding risk from ethnic stratification and the involvement of several genes with low effects though methods are now in place that partially address some of these problems[19].

Potential Longevity Pathways and Genes

The candidate gene approach has extensively been applied to study the effect of single gene on lifespan using experimental animal models such as worm (C. elegans), fruit flies (Drosophila) and mammals (Mouse)[20]. Such studies have been premised on the fact that ageing/longevity could at least in part be explained by inheritance, and consider one major question that was of interest: What is the genetic basis for the wide heterogeneity in lifespan? These model organisms have been the workhorse for genetic study of this question and provide the basis for much of our conceptual understanding of fundamental aspects of genetics of complex traits such as longevity and alcohol dependence[14,21,22].

The studies from the use of the models suggest the existence of evolutionary conserved networks that regulates lifespan and affect longevity across species. Using these organisms, many pathways having human orthologues including those encoding cellular regulation, caloric restriction [sirtuins 2-like protein 1/3 (SIRT1, SIRT3)], stress resistance and oxidative damage [insulin, Insulin Growth Factor 1 (IGFR1)] and DNA repairs [Lamin A (LMNA)], insulin signaling [insulin, IGF1R, Forkhead Box O3A (FOXO3A)], inflammation [Toll-like receptor (TLR), C-reactive protein (CRP), interleukin-6 (IL-6)], telomeres and telomerase [human telomerase (htR), Dyskeratosis Congenita 1 (DKC1)] and lipid metabolism [Apolipoprotein E

(APOE)] have been shown to critically modulate life span[14, 23-25]. Other known pathways/molecules known to be involved in ageing and ageing-related processes include telomere and mitochondria chromosomes that have been well reviewed in a recent study[14]. It is noteworthy that many genes encoding these pathways have been previously reported to be implicated in other complex phenotypes such as Alzheimer's disease[26], indicating that ageing (and possibly longevity) occurs as a result of pleiotropic effects of genes that modulate other fundamental events. Of importance is to note that many of the genes and pathways mentioned above have been found to be affected by gender and thus possess different influences on the probability of achieving longevity in men and women[27]. For instance, there exist gender differences in the effect of insulin/ IGFR1 signaling pathway on the reproductive or hormonal system suggesting that variants that affect genes in this pathway are gender-specifically enriched or depleted as the populations age[28].

Role of Epigenetics in Human Ageing and Longevity

The term epigenetic refers to changes in gene expression that are heritable but do not entail a change in DNA sequence[29,30]. Epigenetic changes involve genetic control by factors that can cause changes to genes that are passed down through generations and that these alterations can affect susceptibility to certain diseases. Epigenetic processes involving DNA methylation, histone modification, miRNA expression etc. can be evaluated in terms of their overall impact on expression changes for a given gene[31,32]. Recent developments have shown that the variations in epigenetic alterations might have an important role in many complex traits including addictive diseases, type-2 diabetes, cardiovascular and autoimmune diseases and obesity[33-35]. These alterations cause modifications of chromatin conformation which may also play an important role in cellular senescence, human tumorigenesis and several age-related diseases[36-40] thus providing novel insights into the actions mediating all of these traits at nucleosomal level in relation to gene expression. Indeed, global decreases in DNA methylation with some site specific hypermethylation that could be regulated by age-dependent changes in DNA methyltransferases have been associated with ageing[32]. Gentilin and co-workers in a genome-wide methylation analysis of centenarians and centenarians' offspring showed evidence of DNA methylation profiles specific for ageing and longevity. They found genes involved in nucleotide biosynthesis, metabolism and control of signal transmission as being differentially methylated between centenarians' offspring and offspring of both non-long-lived parents, suggesting a role for these genes in human longevity. The study also found ageing-associated DNA methylation to be predominant among genes involved in the

development of anatomical structures, organ and multicellular organisms and in the regulation of transcription40. Epigenetic modifications can be the result of stress or diet[29,41,42].

Although precise targets for epigenetic modifications during ageing are unknown, this is an area with great potential, because epigenetic-driven alterations in transcriptional expression as a result of diet or lifestyle are thought to contribute to lifelong health[41]. In fact, some histone deacetylases, like sirtuins, are known to modify epigenetic patterns[29]. Notably, while the epigenetic role of nutrients in the modulation of ageing remains unknown, there is a strong epigenetic link between nutrition and longevity[43]. It is noteworthy that ageing and longevity is at least in part governed by epigenetic mechanisms and an increased understanding of all ageing-related events that are driven by these mechanisms will allow for the development of novel epigenetic-based diagnostic, preventive and therapeutic strategies for ageing and age-related diseases in the near future.

Role of Environment in Human Ageing and Longevity

Environmental factors that may influence longevity include nutrient availability, lifestyle choices, where we live, stress etc. (Figure 1). A vast amount of literature showing these environmental influences on health, longevity, and ageing exists. These environmental influences can be observed from an early stage with long-lasting effects. For instance, severe childhood stress and neglect, and poor early nutrition can increase predisposition to late-life diseases such as cardiovascular disease[44] and mortality[45]. Indeed poor dieting with a lack of exercise has been found to be the main cause of many cardiovascular diseases which shortens life span[46,47]. Notably, the most widely studied dietary manipulation of ageing is caloric restriction (CR) which involves restricting the food intake of organisms normally fed ad libitum without causing malnutrition. CR is the only dietary intervention shown to date to increase longevity and modulate the process of ageing in several model organisms[25,48]. Interestingly, CR is already being used as a paradigm for developing substances that mimic its life-extension properties and might therefore have therapeutic value[48]. Research in mice and rats has shown that CR can extend longevity by up to 50%, delay physiological ageing and postpone or reduce the morbidity of most age-related diseases[49].

Several biomarkers of CR such as body temperature and insulin levels are associated with human longevity[50]. Indeed, CR has been reported to lower body temperature in men and women undergoing CR for an average of six years[51]. However, despite the beneficial effects of CR in health and longevity, CR in mammals is associated with a myriad of negative

consequences including reduction in fecundity, muscle mass, and wound healing ability as well as increased susceptibility to infections[25]. Finally, the mechanisms governing CR lifespan extension has been a subject of debate. A hypothesis is that CR exerts its effect through hormonal changes that affect cells and induce a survival response[52].

Report from the Centres for Disease Control and Prevention of the United States Department of Health and Human Services[53] has indicated that successful aging is largely determined by individual lifestyle choices and not by genetic inheritance. The healthy lifestyle factors that can modulate ageing and extend lifespan include regular physical exercise, rich and proper diet, moderate alcohol use, smoking cessation, adequate sleep and good sleep hygiene. These are important for the prevention of many chronic diseases (e.g., coronary heart disease, type2 diabetes, obesity), disabling conditions (e.g., osteoporosis, arthritis), and chronic disease risk factors (e.g., high blood pressure, high cholesterol).

Possible Gene-Environment Interaction in Longevity Phenotype

Longevity occurs due to randomness, environmental and genetic determinants, and interactions within these three domains of causation (Fig 1). From this perspective, while it is believed that early life environment can affect ageing and longevity; these effects are most likely mediated by gene (G) x environment (E) interactions. Indeed, not all subjects exposed to the adverse effect of the environmental variables listed in figure 1 suffer from age-related diseases or die prematurely indicating that people differ widely in their resilience to the effects produced by those factors. While genetic variation is likely to account partially for much of the differential lifespan phenotype, its interaction with environmental risk factors for lifespan cannot also be ruled out. Interestingly, one possible illustration of the complex interrelationship that exist between genes and environment could be seen from a GWAS data that reported that very long lived individuals share the same risk alleles for cardiovascular diseases, cancer, type2 diabetes than younger controls from the same population suggesting that human longevity is not compromised by the cumulative effect of a set of risk alleles for common diseases[54]. There is thus the plausibility of the existence of complex interaction of not only between favorable and deleterious alleles but also that of the environment versus the two contrasting alleles. It is however, noteworthy that the analysis and interpretations of observed G x E interactions is often influenced by factors such as choice of study design, sample size and genotyping technology[55]. G x E effects within the context of longevity could be modeled for several genes including growth hormone receptor (GHR), SIRT1, IGF1R, APOE, and FOXO3A (see above). Notably, a number of these genes are part of nutrient-sensing

pathways that regulate growth and development, including the insulin/IGF1/GH pathway[56, 57]. It is equally noteworthy that certain age-related diseases such as cancer[58], Alzheimer's disease[59], and autoimmune diseases[60] can be treated by targeting IGF receptors through lowering of IGF signaling. Thus, these ageing-related genes not only modulate response to environmental signals, such as food availability but also act in signaling pathways that if explored and understood could help in designing therapeutic intervention.

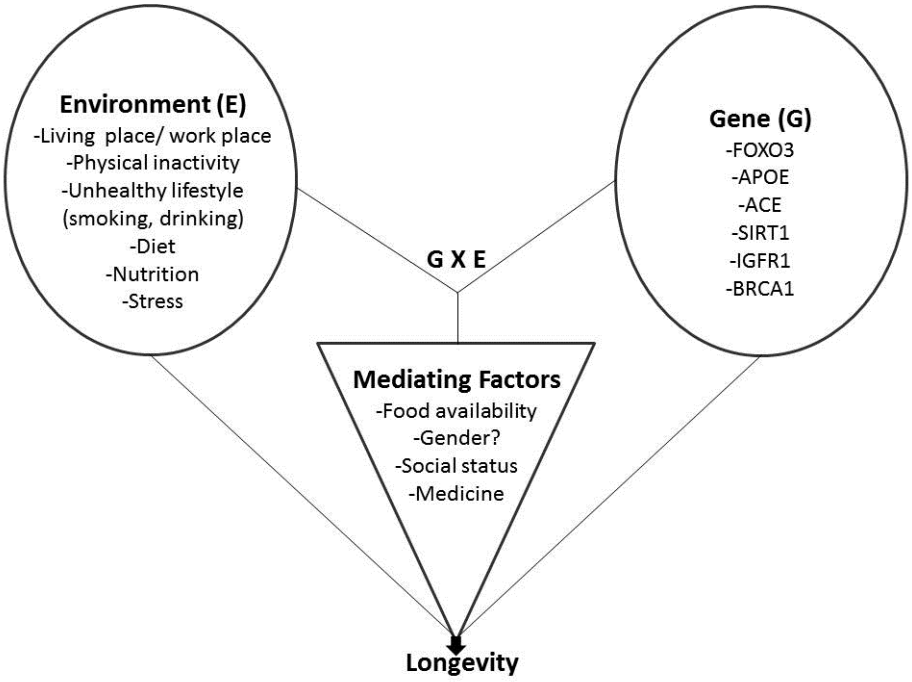

Figure 1. Possible model for interactive effects of genetic and environmental risk factors for longevity?

The mechanism by which CR (discussed above) modulates ageing has been shown to be mediated by genes and signaling pathway in model organisms. Interestingly, research focusing on identifying genes associated with life-extending effects of CR has found one gene called GHR that mediates CR lifespan effect in mammals[61]. Fairly recent data from subjects with GHR deficiency showed decreased mortality from cancer and type2diabetes but increased cardiac disease mortality[62] suggesting that ageing-related genes may have

pleiotropic effects on CR lifespan extension. Thus while targeting these genes may have beneficial effects in one disease, they may be detrimental to another age-related disease. Other genes shown to mediate life-extending effect of CR include sirtuins. Overexpression of sirtuins in yeast has been shown to extend lifespan while CR failed to extend the lifespan of *Sir2* mutants[63]. Interestingly, resveratrol, a plant hormone that can activate *Sir2* and usually found in high concentrations in red wine, has been argued to have implications for healthy life and for establishing wellness[64]. Notably, resveratrol is known to activate SIRT1, a homolog of *Sir2* in mammals, and to increase survivorship of mice on a high-fat diet[65]. However, the effect of SIRT1 and resveratrol on mammalian aging and CR are controversial- resveratrol does not directly activate SIRT1[66].

APOE is one of the first genes associated with human longevity and is involved in lipid metabolism and cholesterol transport. APO E has three major and more than thirty minor isoforms. The three common alleles are epsilon (*ε*) 2, 3 and 4 producing three homozygous (*ε2*/*ε2*, *ε3*/*ε3* and *ε4*/*ε4*) and three heterozygous (*ε2*/*ε3*, *ε3*/*ε4* and *ε2*/*ε4*) genotypes[67]. The difference between the alleles lies at two amino acid residues 112 and 158; with the most common allele *ε3* having cysteine and arginine at these residues, respectively, while *ε2* has cysteine and *ε4* arginine at both locations[68]. The minor isoforms of *APOE* have mostly been linked with age-related diseases such as cardiac disease and AIzheimer's disease (AD)[69,70]. *Carriers of APOE* ε4 allele harbor an increased load of β-amyloid (Aβ) that is thought to be a *major instigator* AD development. Interestingly, healthy lifestyle factors may reduce AD risk by directly mitigating Aβ pathology[71,72].

Besides, the relevance of epsilon 2, 3 and 4 alleles of the APOE gene in human longevity has recently been reinforced[73]. Feng and colleagues[74] however, did not find an association of *ε2* allele with longevity probably due to extreme variability of APOE allelic frequencies in ethnic groups. Indeed, survival to advanced age has been somewhat varied among carriers of the *ε* 2, 3 and 4 alleles, most notably in the Caucasian populations[67, 69, 73, 75, 76].

FOXO3A is a FOXO is a downstream transcription factor involved in the insulin/IGF-1 pathway known to modulate lifespan across species. It is a homolog of dFOXO (Drosophila) and of daf-16 (C. elegans)[77]. In C. elegans for instance, daf-16 has been shown to regulate several genes involved in stress resistance, innate immunity, detoxification and metabolic processes[78]. A strong association between FOXO3 and human longevity has also been reported[79], a finding consistently replicated in other studies involving different populations[24]. The association of FOXO3 and human longevity may be moderated by diets and hormones as FOXO genes are

known to respond differently to nutritional and hormonal factors, suggesting a mechanism for the regulation of FOXO-dependent gene expression by these factors[80]. Thus, the mediating effect of nutrition on this longevity gene adds to the accumulating evidence that gene-environment interplay is very salient to human ageing and longevity.

Conclusions

It is thus clear that the development of longevity phenotype is not caused by a single genetic locus or simple molecular event but by multiple genes or complex molecular events and an interaction between those events and several environmental risk factors. Indeed, genes can influence the probability of stress (an environmental variable) exposure leading to G x E correlation which perhaps contaminate the genetic and environmental effects of longevity and culminate in its G x E interaction interpretation difficulties. Disentangling this relationship is complex and requires the use of model organisms that offer the possibility of controlling not only the environmental influences modulating gene effect but also the confounding problems of G x E correlation. In Drosophila for instance, the expression of genes for lifespan has been shown to vary as a result of G x E interaction and such behavior noted to be strongly affected by environment during development [81]. Finally, the recent research employing the high-throughput technologies in ageing research has caused a shift from single locus study to genome-wide approaches, thereby allowing the identification of genetic variations and quantifications of molecular events at the level of mRNA, protein and metabolites and could help in developing network approaches that test target combinations resulting in the emerging paradigm of network pharmacology82,83 and systematic drug design strategies in ageing field84-86. Therefore, network approaches to both ageing and pharmacology are promising future avenues87, 88 and promise to increase our understanding of the molecular mechanisms underlying individuals' lifespan.

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Correspondence Address / Yazışma Adresi
Awoyemi Abayomi Awofala
Tai Solarin University of Education
Department of Biological Sciences
Ijagun, Ogun State, Nigeria
e-mail: awofalaaa@tasued.edu.ng

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