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Review article

The genetics of exceptional longevity: Insights from centenarians

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ABSTRACT

As the world population ages, so the prevalence increases of individuals aged 100 years or more, known as centenarians. Reaching this age has been described as exceptional longevity (EL) and is attributed to both genetic and environmental factors. Many genetic variations known to affect life expectancy exist in centenarians. This review of studies conducted on centenarians and supercentenarians (older than 110 years) updates knowledge of the impacts on longevity of the twenty most widely investigated single nucleotide polymorphisms (SNPs).

Contents

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1. Introduction

According to a Global AgeWatch Index report from *HelpAge International*, 12% or 868 million persons of today's world population of around 7 billion is aged over 60 years [1]. Human longevity is typically defined as reaching an age of ≥85 years whereas the term exceptional longevity (EL) is reserved for individuals aged ≥100 years, otherwise known as centenarians [2]. EL may be viewed as a threshold trait since it is only expressed by a limited number of individuals (0.7–1/10,000 as the global average) and is the consequence of "successful" aging [3]. Recent research efforts reflect an increasing interest in addressing the factors that determine EL. The subjects examined in these studies have been centenarians and even supercentenarians (SC) defined as those older than 110 years [4]. Such SCs are extremely rare and cited frequencies have been one in 5 million in the western world and a lower frequency in developing countries [4]. Since the end of the 20th century, numbers of centenarians and SCs have increased dramatically, and it is foreseen that these numbers will continue to rise in most countries [5,6].

Aging is a universal phenomenon that affects all animal species and is often described as the outcome of interactions among genetic, environmental and lifestyle factors with wide variation in lifespan between and within species. The explanation of human longevity and how to achieve this desirable phenotype remain among the principal challenges of biology and medicine. Aging is the product of primary aging and secondary aging [7]. Being genetically programed, primary aging is uncontrollable and irreversible whereas secondary aging is a biological process in which physical structure and biological function deteriorate over the years [8]. This last process is susceptible to some control since it is mediated by lifestyle, social, and environmental factors [8]. Thus, aging is determined by complex interactions between genetic and environmental factors. Epigenetic factors (i.e., stable hereditary changes in gene expression patterns that do not lead to a modified DNA sequence) [9] play an important role by influencing the trend towards longevity by up to a quarter [6]. In effect, the "epigenomics of aging" is a promising research topic and studies have compared normal and non-normal ageing by addressing the complex dynamic regulation of primary and secondary aging [10,11].

Many genetic variations that are known to affect life expectancy exist in centenarians [7]. These variations include mutations or polymorphisms, which occur at different frequencies within a population [12]. Genetic variability is mainly determined by single nucleotide polymorphisms (SNPs), and these are the most widely distributed genetic markers in the human genome. In prior work, we addressed the issue of whether centenarians could be genetically predisposed to a lower disease risk by examining genotype scores for 62 genetic variants (mutations/polymorphisms) related to cardiometabolic diseases, cancer or exceptional longevity. Our findings indicated a lower genetic predisposition for cancer in Spanish centenarians possibly associated with exceptional longevity [3]. Human longevity is at least in part genetically determined, with an estimated heritability of 0.20–0.30 [13–15]. A representative population-based study of 2872 Danish twin pairs born between 1870 and 1900 estimated that the heritability of the adult lifespan was 0.26 in men and 0.23 in women [14]. Importantly, the heritability of longevity increases with age, in that a substantial increment is produced for each 10 year increase in the cohort's age of death [16]. The effect of inheritance on lifespan seems most apparent in centenarian and supercentenarian populations [17,18]. The heritability of living to at least 100 has been estimated at 0.33 in women and 0.48 in men [18]. In The New England Centenarian Study, male and female siblings of centenarians were noted to show a 16.95 (95% CI, 10.84–23.07) and 8.22 (95% CI, 6.55–9.90) times greater chance, respectively, of living to an age of 100 compared with individuals comprising the 1900 US birth cohort [17].

This review updates our knowledge of genetic factors affecting the EL phenotype. While an understanding of lifestyle and environmental factors is maximizing efforts to prevent disease and optimize health in the general population, the study of the genetic basis of longevity and healthy aging in exceptionally long lived individuals is starting to provide important biological insights.

2. Methods

Electronic databases (Medline, EMBASE, and Web of Science) were searched without language restrictions to identify all publications on genetics and human EL. Inclusion criteria were: (i) publication in a peer-reviewed journal, (ii) human study, and (iii) mean or minimum age of cohort (or at least of one sub-cohort) ≥100 years. Candidate-gene association studies also had to meet at least 3 of the 5 validity criteria proposed by Attia et al. [19]. Reasons for exclusion were: (i) mean age of case group <100 years, (ii) no control group, (iii) overlapping study populations, and (iv) data reported not usable. A large number of genes have been examined to identify significant associations with EL phenotypes in a wide range of population groups. We included all genetic association studies in which the mean or minimum age range of the cohort (or at least of one study cohort in reports including ≥2 cohorts) was ≥100 years. Each SNP mentioned in the studies was then analyzed for possible associations with EL, identifying the 20 most studied SNPs of the 21st century.

3. Results and discussion

The genetic contribution to human EL likely involves modest effects of many genes. Some authors propose selection for longevity-associated variants which afford protection against basic mechanisms of aging besides offsetting the deleterious effects of genetic and environmental factors [18]. However, it remains unknown how genetic factors and their interactions with modifiable behavioral and environmental factors contribute to human EL. The genetics of EL has been mapped through candidate gene analysis, linkage and linkage disequilibrium mapping, copy number variation and more recently, exome and whole genome sequencing. The 20 most widely investigated SNPs identified in EL are provided in Table 1.

3.1. ACE *I/D (rs1799752)*

The insertion/deletion (I/D) polymorphism of the gene *ACE* (located on the long arm of chromosome 17 at locus 17q23.3), rs1799752, is defined as the presence (insertion, I-allele) or absence (deletion, D-allele) of a 287 bp fragment in intron 16 [20]. Alleles D and I of the *ACE* I/D polymorphism have been linked to higher and lower ACE (angiotensin converting enzyme) activity respectively [21–23]. The role of ACE in the renin–angiotensin–aldosterone sys-