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Review

Historical demography and longevity genetics: Back to the future

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ABSTRACT

Research into the genetic component of human longevity can provide important insights in mechanisms that may protect against age-related diseases and multi-morbidity. Thus far only a limited number of robust longevity loci have been detected in either candidate or genome wide association studies. One of the issues in these genetic studies is the definition of the trait being either lifespan, including any age at death or longevity, i.e. survival above a diverse series of thresholds. Likewise heritability and segregation research have conflated lifespan with longevity. The heritability of lifespan estimated across most studies has been rather low. Environmental factors have not been sufficiently investigated and the total amount of genetic variance contributing to longevity has not been estimated in sufficiently well-defined and powered studies. Up to now, genetic longevity studies lack the required insights into the nature and size of the genetic component and the optimal strategies for meta-analysis and subject selection for Next Generation Sequencing efforts. Historical demographic data containing deep genealogical information may help in estimating the best definition and heritability for longevity, its transmission patterns in multi-generational datasets and may allow relevant additive and modifying environmental factors such as socio-economic status, geographical background, exposure to environmental effects, birth order, and number of children to be included. In this light historical demographic data may be very useful for identifying lineages in human populations that are worth investigating further by geneticists.

Contents

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1. Introduction

During the past 200 years human life expectancy at birth significantly increased in western societies, with record female life expectancy increasing from 45 years in 1840 to 85 years in 2015 (Oeppen and Vaupel, 2002). Around 1950, even the oldest old (age 85 or older) started to show a pattern of extended life expectancy and today they are the fastest growing segment of older people (Oeppen and Vaupel, 2002). This means that populations not only survive to higher ages than in the past, they also have a lower mortality rate, during their young and middle years (Watcher and Finch, 1997). Remarkably, the survival of a select few persons stands out of an otherwise aging population (Christensen and Vaupel, 1996). These persons were extremely long-lived and, most of all, showed little to no signs of age-related disease, allowing them to have extremely long and healthy lives (Andersen et al., 2012; Ash et al., 2015; Christensen et al., 2008; Evert et al., 2003). Research into first-degree relatives of these long-lived individuals showed that they also had extremely long and healthy lives compared to relatives of individuals with more normative ages at death (Pedersen et al., 2017; Perls et al., 2002). Hence, the familial component, including both genetic and environmental contributions, seemed to play a key role in gaining more knowledge about factors involved in healthy aging and in the capability to survive into extreme old ages (often called longevity).

In the literature, the familial component of human longevity has been investigated using survival to extreme age and age at death as phenotypes of survival (see Table 1). The former actually refers to longevity whereas the latter refers to individual or population based lifespan. Both definitions are often used in the context of longevity research which is confusing and incorrect. Another complication is that most studies exclude infant and child mortality by applying a lower limit age threshold when considering the lifespan of a population or group of individuals. Unfortunately, there is no consensus on the age threshold for longevity studies. As a result of both the inconsistent use of terminology and different lower and upper limit age thresholds, the comparison of longevity studies is generally problematic (Sebastiani et al., 2015). We will refer to longevity as survival into extreme old ages whereas lifespan refers to age at death related measures (see Table 1 and Fig. 1).

Progress in longevity research is also hampered by the fact that longevity is likely dependent on an interplay between combinations of multiple genes and environmental factors (Christensen et al., 2006; Deelen et al., 2013; Finch and Tanzi, 1997; Kirkwood et al., 2011; Shadyab and LaCroix, 2015) which makes it difficult to separate environmental from genetic influences. In fact, environmental influences likely moderate genetic effects on longevity (Lewontin, 1974; Montesanto et al., 2017; Rose, 2006). Hence, in this review we describe how historical genealogical data can be used to study familial longevity by including family history information to identify longevous families with a high potential for genetic analysis, such as Next Generation Sequencing (NGS). We start by discussing the state of the art of genealogical heritability and segregation studies in the context of lifespan and longevity. Next we discuss the influence of environmental factors in longevity research, and finally we propose how historical genealogical and demographic data, and the results of genealogical studies can be included in genetic longevity research.

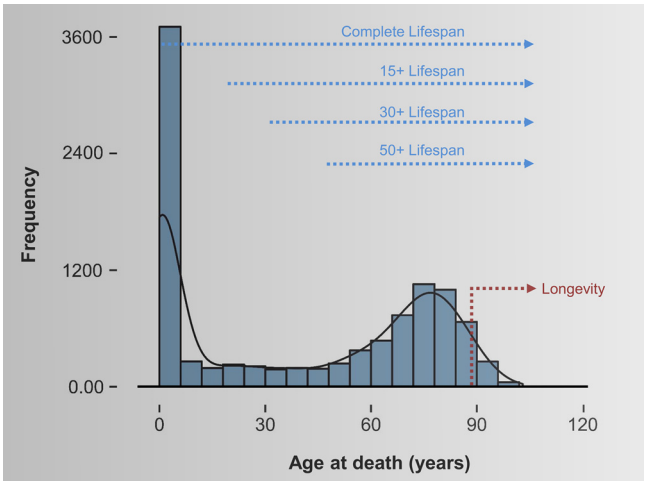

Fig. 1. difference between lifespan and longevity.
Figure is based on data from the Historical Sample of the Netherlands (1860–1875).
–This figure illustrates the distribution of "age at death" in the form of a histogram combined with a density plot. The bars in the histogram represent the number of individuals who died at the age depicted at the x-axis. The line is a density line representing the same concept as the bars.
–The x-axis represents age at death groups for HSN research persons born between 1860 and 1875
–The y-axis represents the number of individuals who died in the different age at death groups
–The distribution depicted in this figure is used to illustrate the difference between lifespan and longevity on an individual level in terms of the place of an individual within the distribution

2. Heritability of longevity has not been established yet

The broad sense heritability (H^2) of a trait can be considered as the upper limit for genetic studies, where heritability coefficients can be seen as a progress indicator, indicating whether after identification of a first gene set for a trait, additional genes may still be determined. Heritability coefficients are differentially interpreted, depending on the type of data used for analysis. When estimated in genealogical data, heritability coefficients provide an estimation of the familial influence on a trait in which the combined effects of genes and shared environment within families are difficult to separate. As a consequence, heritability estimates depend on the environmental context (Lewontin, 1974; Rose, 2006). Twin studies are more suitable than other genealogical studies to provide a first estimate of the influence of genetic, shared, and non-shared environmental influences on a trait. In practice, studies often report the narrow sense heritability (h^2), which is solely based on additive effects (see Table 3 for a summary of key quantitative genetics concepts).

Research into siblings of centenarians showed that persons with a centenarian sibling have a four to eight times higher chance of becoming a centenarian as compared to persons with a sibling who died at a normative age (Perls et al., 2002). A study into parent – offspring relations focused on parents belonging to the top 1 percent of their birth cohort and shows that these parents have a recurrence risk of 2.31 to have children who also belong to the oldest 1 percent of their birth cohorts (Kerber et al., 2001). Similarly, long-lived parents (>95th percentile) have a greater chance of having offspring who also live up to the 95th percentile or above (Gudmundsson