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Brian de Vries

GENERATION

SEE *Cohort.*

GENETIC INFLUENCES, LATER LIFE

Genetic influences are the influences that can be attributed to heredity (family likeness). Heredity is the passing of characteristics (traits) from parents to offspring. Genetic influences in later life are attributed to traits related to aging such as life span and longevity, age at menopause, age at onset of specific diseases in late life (Alzheimer's disease, heart disease, and so on), physical health and cognitive functioning in later life, rate of aging (estimated through tests for biological age), rate-of-change traits, and biomarkers of aging (Finch, 2007).

Genetic influences are also related to effects of the fundamental chemical units of heredity called genes. A gene is a segment of deoxyribonucleic acid (DNA) carrying coded hereditary information. The number of gerontogenes (genes involved in the aging process) remains to be established, but there are no doubts of their existence. For example, in humans one of the forms of a gene coding apolipoprotein E (APOE2) is associated with exceptional longevity (more prevalent among centenarians) and decreased susceptibility to Alzheimer's disease (Finch, 2007; Martin, Bergman, & Barzilai, 2007).

Genetic influences operate through the mechanism of gene action—the way in which genes produce their effect on an organism by influencing biochemical processes during development and aging. Many of the genes within a given cell are inactive much or even all the time (repressed). Different genes can be switched on or off depending on cell specialization (differentiation)—a phenomenon called differential gene expression. Gene expression may change over time within a given cell during development and aging. Changes in differential gene expression are vitally important for cell differentiation during early child development, but they may persist further in later life and become the driving force of the aging process.

Although genes determine the features an organism may develop (genotype), the features that actually develop (phenotype) depend upon the complex interaction between genes and their environment, called gene–environment interaction. Gene–environment interactions are important because genes produce their effects in an indirect way (through proteins), and, therefore, the ultimate outcome of gene action may be different in different circumstances (Ryff & Singer, 2005). Although genes do not change over the life course (creating the impression of causal links), many traits in later life demonstrate very high environmental plasticity; that is, they can be modified in response to an environmental change (Ryff & Singer, 2005). Older adults on average experience poorer health compared to younger adults, so genetic contribution to health, functional status, and cognition are among the most thoroughly studied traits in later life.

STUDY METHODS AND DESIGNS

Most studies of genetic influences use quantitative genetics (or ACE) models to separate the sources of phenotypic or observed variability into an *additive* genetic

component (A), a *common* or shared environment component (C), and a nonshared *environment* element (E). Shared environmental influences are shared nongenetic factors that are transmitted from parents to offspring or are shared by the members of the same family (such as lifestyle or diet). Nonshared environmental influences are nongenetic factors that are different among family members. The genetic contribution to phenotypic variability of trait is measured using heritability estimates. Heritability estimates represent the proportion of phenotypic variation of trait that can be explained by genetic effects. A heritability value of 1.0 (or 100%) means that the trait is fully genetically determined, whereas a value of 0 means that the trait is fully environmentally determined.

Quantitative genetics uses a number of designs in the study of genetic influences, including family design, twin design, and the adoption method. Family design compares the incidence of disease (or other trait) among biological and nonbiological relatives of an affected individual (called proband). The famous statistician Karl Pearson (1857–1936) and Alexander Graham Bell (1847–1922), the inventor of the telephone, were among the first researchers to try to estimate the contribution of genetic factors into the human life span at the beginning of the 20th century (see review in Gavrilov, Gavrilova, Olshansky, & Carnes, 2002). The first comprehensive studies of familial resemblance and longevity go back to the 1930s when the American biostatistician Raymond Pearl published his seminal book, *The Ancestry of the Long-Lived*, which showed that close relatives of nonagenarians (persons in their 90s) live longer than relatives of shorter lived persons (Pearl & Pearl, 1934). This initial finding was later replicated by numerous studies of persons with exceptional longevity, including early 21st century studies of centenarians (Martin et al., 2007).

The twin design is based on the comparison of identical (monozygotic) twins and fraternal (dizygotic) twins. Monozygotic twins are assumed to be genetically identical to each other because they developed from the same fertilized egg. Dizygotic twins are formed from two different fertilized eggs and have only half of their genes in common. If a trait is genetically influenced, then monozygotic twins should show a closer resemblance to each other in regard to that trait compared to dizygotic twins. Franz J. Kallmann was the first researcher to apply twin design to the study of late-life traits and to conduct a survey of old twin pairs (Kallmann & Sander, 1948).

The adoption method is a quasi-experimental design based on cases in which children are adopted away from their biological parents early in life. This gives researchers the opportunity to separate the effects of nature and nurture. The Swedish Adoption/Twin Study of Aging is probably the largest repository of data on adopted twins (Pedersen & Svedberg, 2000).

In addition to the methods of quantitative genetics, molecular genetic methods are used to identify specific genes responsible for genetic influence. In molecular genetic studies of human aging traits, the gene association studies remain the most common research approach (De Benedictis et al., 2001). In these studies the effect of candidate genes on longevity is analyzed by comparing gene frequencies between affected individuals (cases) and unaffected control individuals. The comparison of candidate gene frequencies among centenarians and younger controls is a typical example of such studies. Another molecular genetics approach—the genome-wide linkage scan of genes—is a relatively new direction of research. Linkage analysis is a mapping of genetic loci using observations of related individuals (pairs of affected and nonaffected siblings, for example). This direction of research has a potential for obtaining interesting results, although the success of genome-wide scans of complex human diseases requires large sample sizes and considerable effort and expense.

In addition to common phenotypic traits (such as the presence or absence of disease), the genetic epidemiology of aging incorporates age in the specification of traits under study. The traits that are specific for later life are survival traits and rate-of-change traits (Hadley et al., 2000). A survival trait is defined in terms of the specific age interval over which an individual is at risk for a specific outcome. For example, early-onset and late-onset variants of Alzheimer's disease are associated with different genes and modes of action. Rate-of-change traits are defined as changes in physiological, cognitive, or behavioral traits over a period of time. The study of genetic influences on rate-of-change traits is a rapidly developing area of research in the early 21st century (Pedersen & Svedberg, 2000).

MAJOR RESEARCH FINDINGS

Longevity is one of the most widely studied broad survival traits. It was shown that siblings and parents of persons with exceptional longevity have significantly lower mortality compared to population-based controls and that the offspring of long-lived parents live longer than the offspring of short-lived parents (Gavrilov, Gavrilova, Olshansky, & Carnes, 2002; Martin et al., 2007). Genetic influences on longevity found in family studies were confirmed in twin and adoption studies (see Gavrilov et al., 2002). Although a strong familial clustering of longevity is now a well-established fact, heritability estimates for life span using standard methods of quantitative genetics are moderate—20% to 30% (Cournil & Kirkwood, 2001).
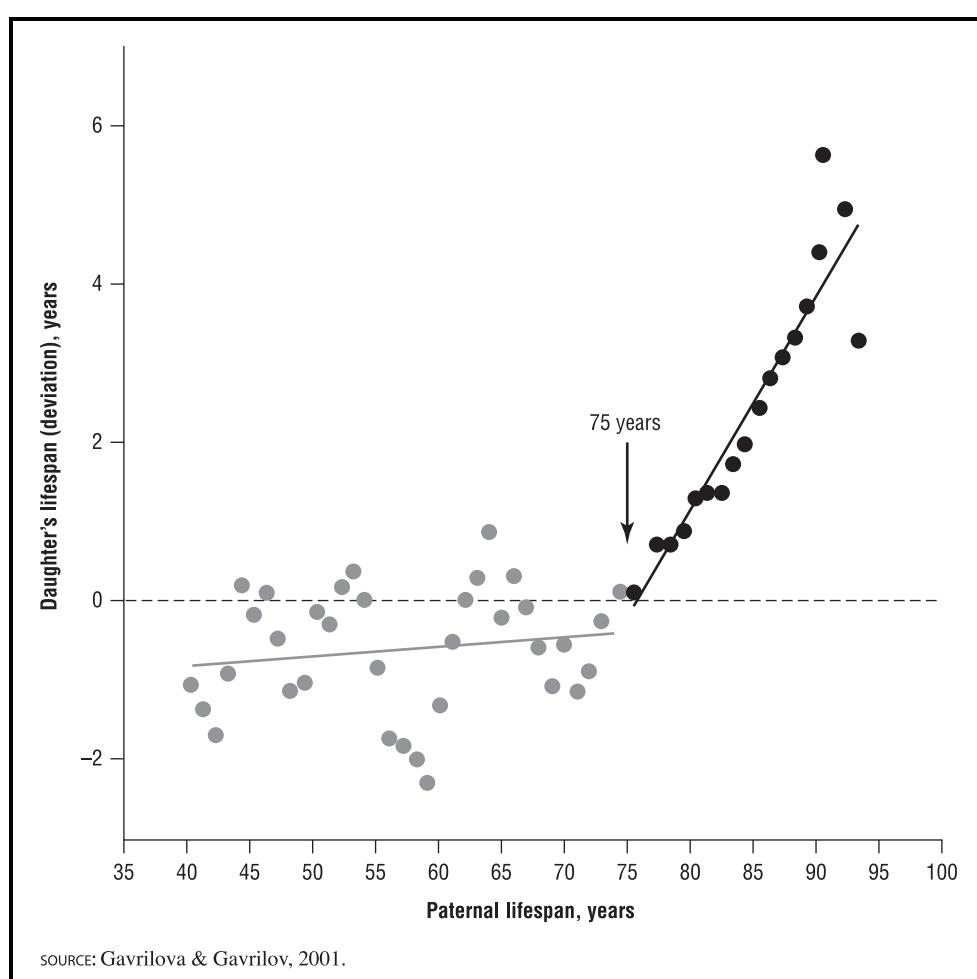
Figure 1. *Daughter's life span (deviation from the cohort mean) as a function of paternal life span. Based on the data for 5,779 daughters from European aristocratic families born between 1800 and 1880 who survived to age 30. Data are smoothed by a 5–year moving average.* **CENGAGE LEARNING, GALE.**

Heritability estimation by standard methods of quantitative genetics is based on the assumption of linear dependence between offspring and parental traits. A study of more than 10,000 adult men and women from the European aristocracy, however, demonstrated that familial resemblance in life span between parents and children is essentially nonlinear (see Figure 1): very small when parents live shorter lives (30 to 70 years) and very strong in the case of longer lived parents (80+ years), suggesting an unusual nonlinear pattern of life-span inheritance (Gavrilov et al., 2002). These findings may explain the existing longevity paradox: Although the heritability estimates for life span were reported to be rather low (Cournil & Kirkwood, 2001), it is well known that longevity runs in families (Martin et al., 2007). A 2006 study of Danish and Finnish twin cohorts confirmed that genetic influences on human life span are minimal before age 60 but increase thereafter (Hjelmborg et al., 2006).

A review of gene–longevity association studies revealed that different studies often produced inconsistent and even contradictory results (De Benedictis et al., 2001). Most studies of gene–longevity association are based on case-control studies of centenarians, in which the proportion of a certain genotype among long-lived individuals is compared to the same proportion in a presumably shorter lived control group (usually persons of middle age). If the proportion of a particular genotype is higher among long-lived individuals compared to the control group, then it is assumed that this genotype may be associated with longevity. The association of a genotype with longevity in case-control studies is usually measured using odds ratio, which is a measure comparing whether the probability of longevity is the same between two groups. An odds ratio higher than unity means that carriers of a particular genotype have a higher chance of living to 100 compared to non-carriers; alternatively, an odds ratio less

than unity means that carriers of a particular genotype have a smaller chance of living to 100 compared to non-carriers.

The APOE gene is the only one that demonstrated consistency in different case-control gene–longevity studies (Finch, 2007). Apolipoprotein E (APOE) is a protein involved in cholesterol transport that binds to LDL receptors and is crucial to blood cholesterol levels (Finch, 2007). The APOE4 gene variant (allele) was found to be associated with heart disease, Alzheimer's disease, and longevity. APOE3 is the most prevalent allele in human populations, whereas APOE4 may vary and is higher than 15% in northern Europe and among aboriginal populations of New Guinea and Australia (Finch, 2007).

A combined analysis of eight APOE findings showed a net odds ratio for extreme longevity of 0.51 for the E3/E4 genotype compared to the common E3/E3 genotype, implying that the E3/E4 genotype reduces by roughly 50% the chances of survival to extreme ages compared to E3/E3 (Melzer, Hurst, & Frayling, 2007). The prevalence of APOE4 decreases with age because of differential survival—the mortality of E4 carriers is 10% to 14% higher and the mortality of E2 carriers 4% to 12% lower compared to E3/E3 and E4/E2 genotypes. It was estimated that individuals with the E4/E4 genotype may have a life expectancy at age 65 that is 5 years shorter than that of individuals with the E2/E2 and E2/E3 genotypes (Ewbank, 2004). Linkage studies of longevity genes are less common compared to association studies. One genome-wide linkage study of U.S. centenarians found a suggestive locus at chromosome 4, although this finding was not replicated in other populations (Melzer et al., 2007).

Parental age is another genetically linked factor affecting longevity. Children conceived by fathers at older ages have more inborn mutations (Vogel & Motulsky, 1997) and may be at higher risk of Alzheimer's disease and prostate cancer in later life. Daughters conceived by fathers age 45 and older live shorter lives (on average), whereas sons seems to be unaffected, suggesting the possible role of mutations on the paternal X chromosome (inherited by daughters only) in the aging process (Gavrilov et al., 2002).

Most chronic diseases in later life are complex multifactorial disorders. Multifactorial disorders are influenced by multiple genes, often coupled with the effects of environmental factors. Many diseases common to old age, such as late-onset Alzheimer's disease, heart disease, and diabetes, are considered to fall into this category. Most genes associated with multifactorial disorders have low penetrance, meaning that genotype carriers' likelihood of developing the disease is low. Thus, the individuals with disease-related genes do not necessarily succumb to the disease (Ryff & Singer, 2005). With a favorable lifestyle and environment, there is an opportunity for an individual with genetic risk factors to delay and even avoid the disease. For example, in the 1960s and 1970s the population of North Karelia in Finland had very high levels of heart disease and a significant proportion of people carrying mutations predisposing them to familial hypercholesterolemia (high blood cholesterol). However, an intensive community-based intervention program directed at lifestyle improvement significantly percent reduced (by 60% to 70%) heart disease and cancer rates over the span of 25 years (Ryff & Singer, 2005). Thus, the genetic risks of diseases in later life can be substantially reduced by proper behavioral, social, and economic measures.

Alzheimer's disease is the most common cause of severe memory loss at older ages. For late-life forms of dementia, the APOE4 allele was found to be strongly associated with both late-onset Alzheimer's disease and accelerated cognitive decline after age 65 (Finch, 2007). The highest cognitive decline was observed in APOE4 carriers with diabetes, carotid atherosclerosis, and peripheral vascular disease. APOE4 carriers with mild cognitive impairment were two to five times more likely to develop Alzheimer's disease compared to carriers of the most common APOE3 genotype. Another APOE allele, the APOE2, was found to be protective against Alzheimer's disease (Finch, 2007).

Many biomarkers of physiological or functional status including handgrip strength, walk speed, systolic blood pressure, pulmonary function, fasting glucose level, and bone degeneration demonstrate a high heritability at older ages (Melzer et al., 2007). Integral estimates of biological age have also been shown to have a strong genetic component, with heritability estimates ranging from 27% to 57%. Age at natural menopause was found to be highly heritable: Data from the two generations of the Framingham Heart Study showed that the crude and multivariable-adjusted heritability estimates for age at natural menopause were 0.49 and 0.52 (Murabito, Yang, Fox, Wilson, & Cupples, 2005). Sex hormone levels play an important role in health and survival at older ages. Studies of male twins ages 59 to 70 found that plasma testosterone levels have substantial genetic variation, whereas estrogen concentrations were largely influenced by environmental factors.

Cognitive functioning also shows a significant genetic component. Most studies of cognitive abilities in later life were conducted using studies of older twins, which showed that the overall cognitive functioning in older age is highly heritable with estimates of heritability equal to 76% in Danish twins 70 and older and 62% in Swedish twins 80 and older (Melzer et al., 2007).

Researchers have also started to collect information on genetic influences at different ages as well as on rate-of-change traits (Pedersen & Svedberg, 2000). Studies show that phenotypic variability has a tendency to increase with age for the majority of traits because of nonshared environmental effects. Genetic contribution to variability in cognitive abilities shows stability until ages 65 to 70 and declines thereafter. A similar pattern was found for self-rated health. Rate-of-change traits usually demonstrate a lower heritability compared to the absolute levels of studied traits. This was found to be the case for such traits as cognitive performance, body mass index, and lipid and lipoprotein levels. Thus, the rate-of-change traits apparently are not significantly affected by genetic factors.

Gene–environment interactions represent one of the most important and promising areas for the studies of the life course. Gene–environment interactions refer to differential genetic sensitivity to specific environmental factors. Genetic factors often act as effect modifiers (or moderators) when effects of socioeconomic or behavioral factors are analyzed. For example, there is no increase in risk for Alzheimer's disease among persons with head injury if they do not carry the APOE4 gene. For carriers of APOE4, however, head injury results in a tenfold increase in the risk of Alzheimer's disease. Similarly, APOE4 was found to be a risk factor for ischemic heart disease, but this applied mainly to smokers (Ryff & Singer, 2005).

It should be noted that heritability estimates for late-life traits may vary significantly across populations and that populations living in less favorable environments generally demonstrate smaller effects of genetic factors on variability of late-life traits. For example, the heritability of forced respiratory volume in Russian twins was found to be much smaller compared to Swedish twins most likely because of differences in environmental influences between Russian and Swedish samples (Whitfield, Brandon, & Wiggins, 2002).

RESEARCH CHALLENGES AND FUTURE DIRECTIONS

Studies of genetic influences in later life face many methodological challenges. The main problem is that many individuals do not survive to late ages, and this survival is affected by both environmental and genetic factors. Twin studies often suffer from the limitations of cross-sectional design when it is impossible to distinguish selection effects (genetically determined differential survival) from true aging changes (Pedersen & Svedberg, 2000). Studies on exceptional longevity often suffer from the lack of data on living relatives, including parents (Hadley et al., 2000). Inconsistency in the findings of many gene–

longevity association studies may be due to the lack of proper control groups in these case-control studies, because cases (centenarians) and controls (young adults) belong to different birth cohorts with different past histories. Thus, a comparison of centenarians and young adults is susceptible to artifacts resulting from differences in genetic makeup between different age cohorts unrelated to differential survival. The collection of longitudinal data (data from the same individuals over time) for twins and adoptees will alleviate the problems posed by cross-sectional designs and help to discriminate between selection processes and true aging changes. The collection of biomarkers (including genetic markers) that is underway in many population surveys and longitudinal studies in the early 21st century will fill the gap in knowledge about the association between specific genetic markers and later life traits. The most promising areas of research—gene–environment interactions in later life and early life genetic influences on late-life traits—are at the beginning of their development and will shape future life-course research on genetic influences in later life (Pedersen & Svedberg, 2000; Ryff & Singer, 2005).

POLICY ISSUES

The rapid development of molecular genetics and the prospect of individual genome scans raise serious ethical concerns about the proper use of individual genetic information. Should individuals be informed about genetic risks for chronic diseases in later life if this information may result in unnecessary stress? Older persons having genes predisposing them to the risk of certain diseases (such as the APO4 gene) may be unfairly treated by insurance companies. These problems require both the protecting sensitive genetic information and educating the public that having genes predisposing a person to late-onset diseases is not a destiny and that individuals with unfavorable genotypes may never develop the specific disease (Ryff & Singer, 2005). At the same time, knowledge about genetic markers predisposing to late-life diseases may lead to the development of intervention measures specific to individual genetic makeups. Such a personalized approach may eventually become a fixture in medical care.

SEE ALSO Volume 3: *Aging; Dementias; Frailty and Robustness; Life Expectancy.*

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Natalia S. Gavrilova
Leonid A. Gavrilov

GLOBAL AGING

Global aging broadly refers to the process by which the populations of the world's nations are growing increasingly older; indicators of population aging include the proportion of a nation's population that is age 65 or older, as well as trend data showing that the average and median ages of a nation's population have increased over time. Population aging processes throughout the world will have critically important social and economic consequences, including a potential shortage of working-age individuals, heightened demand for costly health care services, adequate housing accommodations and pensions for older adults, and a growing number of older adults relying on their children and grandchildren for social and economic support.

The rapid increase in population aging across the globe signals one of the most important demographic changes in recent history. In the latter half of the 20th century, the world's developed nations completed the demographic transition (Phillipson, 1998). The demographic transition refers to a societal-level shift from high mortality rates and high fertility rates (thus, short life spans and large families) to low mortality rates and low fertility rates (thus longer life expectancies, and smaller families). Countries that proceed through this transition ultimately have relatively high proportions of older persons and low proportions of younger persons (Powell, 2005). This transformation has taken many years to unfold, and is influenced by multiple factors. For example, in Europe and North America, the process of population aging is driven by factors including basic public health measures that steadily reduced the risk of contagious disease and modern medicine that has prolonged lives. In developing nations, by contrast, the demographic transition is still underway. These countries vary widely in how far along they are in the demographic transition; although most developing nations have much younger populations than developed nations, their numbers of older adults are increasing rapidly.

Researchers use a variety of methodological tools to document trends in population aging, and to predict the societal consequences of these demographic changes. Data on population aging processes come from multiple sources. Vital statistics registries, maintained by local governments, track all births and deaths as well as changes in an individual's legal status such as marriage, divorce, and migration (registration of one's place of residence) (Phillipson, 1998). In developed countries with good registration systems (such as the United States and much of Europe), registry statistics are the best data source for enumerating the number of births and deaths in populations (Bengtson and Lowenstein, 2004).

Researchers also use data obtained from population censuses. Censuses are usually conducted by national governments and attempt to enumerate every person in a country (Gavrilov & Gavrilova, 1991). Censuses also gather basic social and demographic information about a