Familial Mortality in the Utah Population Database: Characterizing a Human Aging Phenotype

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We examine the effects of familial longevity and familial mortality on mortality rates for 10 leading causes of death in a Utah Population Database (UPDB) cohort. Familial excess longevity (FEL) and familial standardized mortality ratios (FSMR) were estimated for 666,921 individuals born from 1830 through 1963, who survived to at least age 40. Cox regression analysis shows that familial death and familial longevity have independent effects on cause-specific mortality rates for 10 leading causes of death. A family history of disease increases one’s risk of dying from the same cause, whereas a family history of longevity is protective, except in the case of cancer. Families with greater longevity do not die of causes distinct from other members of the cohort, but they die from the same causes at reduced rates. Individuals from longer lived families have lower mortality from most age-related diseases including heart disease, stroke, and diabetes, but not cancer.

The study of life span has been a central focus of population and evolutionary biologists for a long time (1). A natural preoccupation with human life span developed first with a focus on measuring its heritability (2–5) but usually from data limited in various ways. However, with many replications, and considerable variation in results, a positive case for human life-span heritability has been made. Over time this avenue of investigation has developed to address a wide range of questions regarding the biological parameters of life span, its stages, and its evolution. One notable result is that many studies of longevity now incorporate as a primary aim the identification of genetic factors that contribute to the duration of life. In human studies, for instance, the main themes of current longevity research include the heritability of mortality risks from aging-related diseases (6–9), gene associations with exceptional longevity outcomes (7,10–12), and identification of the risks and protective factors that condition healthy longevity, or what has been termed “healthspan” (13).

To advance the ultimate goal of identifying genetic factors of longevity (13), this study attempts to further articulate the heritable components of phenotypic variation in human aging that affect life span. Here we consider life span as a trait composed of two familial quantities: longevity and mortality. In a large population cohort we identify the 10 most common causes of death, and treat them as phenotypes. We measure individual familial longevity and familial mortality for cohort members, and analyze how familial longevity and familial mortality interact with cause-specific mortality risks and hazard rates with age, and by gender. We examine (i) how family history of death and family history of longevity contribute to life span and (ii) causes of death that commonly conclude it. We focus on deaths in the adult portion of the life span (ages 40–105 years) and causes from age-related chronic diseases—heart disease, cancer, stroke, and diabetes.

Our investigation addresses the potential role of genes in mediating longevity. In studies of aging, the oldest old are often regarded as likely carriers of alleles that predispose them to long life. In truth, however, it is not known whether the excess longevity of the oldest old results from particular gene variants that extend healthspan or from a lack of gene variants that reduce healthspan. Although animal systems have produced evidence of genes directly related to longevity, it is more difficult to measure phenotypic longevity in humans consistently and meaningfully. Therefore, in human studies, the focus is more often on “aging,” with an emphasis on discovering deleterious genes that predispose individuals to age-related fatal diseases.

In this study we measure heritable variation in both disease-specific mortality and longevity. Our approach is to first test whether familial mortality and longevity independently impact mortality risks for specific age-related causes of death. We continue with a further analysis of how variation in familial longevity affects mortality hazard rates with age, for men and women, and for the leading causes of death.

A novel aspect of this study is the exceptional quality and depth of data available from the Utah Population Database (UPDB) to calculate the familial structures of such complex and heterogeneous traits as mortality and longevity. Together with only a few other resources like it (14), the UPDB provides unusual potential for population analyses; the extensive analytical tool development that supports this resource makes them possible.
METHODS

UPDB

Data for this study were drawn from the UPDB, a unique resource housed at the University of Utah and used for biomedical research. The history and collection events that established, have grown, and maintain the UPDB are described in detail elsewhere (15,16). UPDB’s genealogical information originally derived from ‘Family Group Sheets’ describing 170,000 Utah families. These data have been extended, and new individuals and families added, by regular linking to state birth and death records. Vital status follow-up information is provided by periodic linking to state driver’s license information, to data from the Centers for Medicaid and Medicare Studies (CMS), and to the Social Security Death Index (SSDI). Information from two state cancer registries is linked to the UPDB: the Utah Cancer Registry, and the Cancer Data Registry of Idaho. Today the UPDB contains records for more than 6 million individuals, approximately 3 million of whom constitute the linked genealogical network of the database. Genealogical information in the UPDB captures up to 10 generations for some individuals.

Cause of Death Data

Death certificate data for Utah are available in the UPDB with coded underlying causes of death for the years 1904–2003, and include more than 650,000 recorded deaths. International Classification of Diseases (ICD) cause-of-death coding (revisions 6–10) was provided by the Utah Department of Health for certificates recorded from 1957 through 2003. For the years from 1904 through 1956, investigators from a previous project (KRS and DLR) transcribed causes of death from their original text and coded them to ICD-10 codes by using the 2000 Mortality Medical Data System (MDDS) developed by the U.S. Department of Health and Human Services. Underlying causes of death were supplied this way for approximately 75% of the records, and the remainder were coded manually according to the World Health Organization instructions for ICD-10 volume 2.

Study Cohort

A cohort was selected to include all persons born from 1830 through 1963, who have at least one family member in the database. Each member of the cohort lived or died in Utah since 1904, when standardized state death certification was first used. From various data sources we confirmed the vital status to age 40 years of every cohort member. Status was then tracked through later ages from birth, death, or cancer records; driver’s license; or a CMS or SSDI data point. Last observations (death or other) were used as censoring dates in survival analysis. The cohort defined in this way included 666,921 cohort members followed through 2003.

The extensive family histories available in the UPDB allowed us to address familial trait clustering in the population with efficient means of navigating and caching information from these very extensive and intertwined pedigrees. Over the years, we have developed general purpose tools and methods for applying the large and complex pedigree architecture of the UPDB to a variety of genetic and epidemiologic uses (3,17,18).

Familial Standardized Mortality Ratio

Familial standardized mortality ratios (FSMRs) were calculated for all individuals in the cohort, similar to the Familial Standardized Incidence Ratio, or FSIR (19). The FSMR is the observed mortality among family members of an individual, divided by the expected mortality, with weights for relatives \(j\) of a proband \(i\) given by the kinship coefficient (20), the probability that \(i\) and \(j\) share a given gene identical by descent from a common ancestor, \(\rho(i,j)\):

\[
FSMR_i = \frac{\sum_{j \in J} f(i,j) \rho(i,j)}{\sum_{j \in J} f(i,j) \sum_{k=1}^{J} t_{jk} r_{jk}},
\]

where \(J\) is the set of all relatives of \(i\), \(\rho(i,j)\) is an indicator variable (1 if \(j\) dies of the disease of interest, 0 otherwise), \(t_{jk}\) is the time spent by \(j\) in the \(k\)th risk stratum (designated by sex and age), and \(r_{jk}\) is the population risk per unit time for a person in stratum \(k\). FSMR measures an individual’s family history of a trait, and the approach has been shown elsewhere to be a useful predictor of disease risk (17,21,22). Here it is used to measure the familial component of cause-specific mortality.

Familial Excess Longevity

The computation of familial excess longevity (FEL) for each individual is accomplished in two steps. Excess longevity (EL), defined as the difference between an individual’s attained age and the age to which that individual was expected to live incorporating into the model potential confounders of longevity, is estimated for each cohort member. Here we include gender and birth year, although other environmental or behavioral factors that influence life span could be included as well. EL (\(\hat{y}\)) is estimated from an accelerated failure time model in the following manner:

\[\hat{y} = e^{\alpha + \beta_1 \text{gender} + \beta_2 \text{birthyear} + \ldots}\]

where \(\alpha\) is the intercept, \(\beta_1 \ldots \beta_n\) are slope coefficients, and EL (\(l\)) is simply \(y - \hat{y}\), with \(y\) the attained age in years assessed for birth cohorts (e.g., born before 1900) for which exceptional longevity is possible. This is similar to the method described by Bocquet-Appel (23).

FEL (3) is estimated for each cohort member by summarizing the calculated ELs over all of an individual’s family members. Two cohort sampling issues come to bear on this calculation. First, an individual’s FEL is calculated from the achieved longevity of his or her relatives. Therefore, only relatives born before 1900 were included in the computation of FEL, so that by 2003, individuals could have survived to age 105 years, and we could capture survival for the oldest old. Second, FEL is calculated for relatives who lived to the baseline age of 65 years. At 65
years and older, death rates due to age-related diseases more specifically reflect variation in senescence apart from causes of early mortality. We average excess longevity of an individual’s family members, weighted by kinship coefficients, to yield an estimate of FEL:

\[
\text{fel}_i = \sum_{j} f(i,j) \cdot l_j / \sum_j f(i,j),
\]

where \(\text{fel}_i\) is the excess longevity for individual \(i\), \(J\) is the set of all relatives of \(i\), \(l_j\) is the excess longevity of the \(j\)th member of \(J\), and \(f(i,j)\) is the probability that \(i\) and \(j\) share a gene identical by descent from a common ancestor.

**Estimation of Hazard Functions**

Failures due to a specific cause of death were counted only when the cause was given as “primary” on the death certificate; all other deaths were treated as due to another cause and were censored from the death date forward. We began by computing unsmoothed (Kaplan–Meier) hazards by counting the number of deaths in each 1-year interval, divided by the number at risk at the beginning of the interval. In general, the unsmoothed hazard functions were imprecise and the plots difficult to interpret visually. Kernel smoothing also proved unsatisfactory because, at extreme ages, the smoothing function frequently introduced an artificial drop in the hazard rate where none was apparent in the unsmoothed data. To plot smooth hazard functions by category without imposing artificial constraints, we used generalized \(\gamma\) survival regression models stratified by gender and level of FEL. The density of the generalized \(\gamma\) with parameters \(\mu\), \(\sigma\), and \(\kappa\) is:

\[
f(t) = \begin{cases} 
\frac{\gamma^\kappa \exp(\gamma \mu - t)}{\sigma \sqrt{\Gamma(\kappa)}} , & \text{\kappa \neq 0} \\
\frac{\exp(-t^{\gamma/2})}{\sqrt{\Gamma(\gamma)}} , & \text{\kappa = 0}
\end{cases}
\]

its survival function is:

\[
S(t) = \begin{cases} 
1 - \Gamma_{\mu}(\gamma) , & \kappa > 0 \\
1 - \Phi(\gamma) , & \kappa = 0, \text{ and the hazard function is} \\
\Gamma_{\mu}(\gamma) , & \kappa < 0
\end{cases}
\]

\[
h(t) = \frac{f(t)}{S(t)},
\]

where \(\gamma = [\kappa^{-2}]\), \(\Gamma(\gamma)\) is the standard normal cumulative distribution function, and \(\Gamma_{\mu}(\gamma)\) is the incomplete \(\gamma\) function. This method generates shape and scale parameters for each curve estimated, each gender, and each stratum of FEL. Middle and bottom FEL strata were then compared to the top stratum, with tests of significance given for differences in their shape parameters. (Graphs are displayed, but parameter estimates are not reported.)

FEL strata were also compared within a Cox proportional hazards framework. For these Cox models, an individual’s cause-specific mortality hazard rate is specified as a function of FSMR and FEL. All models were fitted using Stata survival methods (24).

**Results**

Table 1 reports the number of deaths recorded in the UPDB for the 10 leading causes among individuals who survived to at least age 40. Unadjusted cause-specific deaths are listed for men and women by decade from 1904 through 2003. We first considered 15 leading causes of death in the

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<td>105</td>
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**Notes:** All individuals studied were born from 1830 through 1963. All cases were deaths among individuals 40–105 years old. Descriptive frequencies of certified deaths in the Utah Population Database (UPDB) for individuals aged 40–105 years, per decade in the study cohort. Unadjusted frequencies are given for the 10 leading causes of death, for male (M) and female (F) gender.
United States in 2003 to establish the overlap in ranking with the same 15 causes in the UPDB. We then narrowed our overview to the 10 causes with sufficient number in the UPDB to reasonably analyze them over the time period. With only minor changes in rank among causes, these 10 are the same in both populations, at this crude level. This list was reduced further for the final analyses, in which we focused on only the four leading causes due to known age-associated disease processes.

Table 2 lists the same 10 leading causes of death in the population for individuals 40 years old and older. The total number of deaths per cause and gender are given. FSMR and FEL are reported as relative risks when both are considered associated disease processes.

For every cause of death and most age groups, mortality rates for FEL groups are ordered so that the group with highest familial longevity has the lowest mortality, and the group with lowest familial longevity has the highest mortality. In the case of cancer, differences among FEL groups are smaller. Table 3 also shows higher mortality rates for men compared to women at all ages, but not without variation among causes. In the case of stroke, for instance, women have higher cumulative mortality rates before age 80, and are similar to men thereafter. This same pattern applies to cancer, where cumulative mortality rates are a bit higher for women than for men before age 80.

In Figures 1–5, we graph estimated hazard functions by FEL strata to help visualize trend differences in mortality. First, hazard functions are plotted for combined causes of death for the cohort, then for the four leading causes—heart disease, cancer, cerebrovascular disease, and diabetes—for men and women separately. On each graph, FEL strata are defined as the top 25%, the middle 50%, and the bottom 25% of the distribution of FEL values.

Figure 1 establishes baseline hazard rates for all causes of death combined in the population, aged 40 and above. First, estimated hazard rates are shown for combined causes of death, but stratified by sex. This graph demonstrates a characteristic mortality pattern of post-transitional populations in which women have greater longevity than men. Here, women have lower mortality hazards through most of the adult life span. Second, hazard rates are shown for combined causes of death, but stratified by FEL level. Here, the top FEL group has the lowest death hazards, the middle group intermediate hazards, and the bottom group the highest hazards over most of the adult life span. For all the leading causes of death combined in this population then, women have lower mortality hazards than men have, and the higher one’s FEL, the lower one’s risk of death at all ages (40–105 years). These patterns hold until about age 90, after which the number of individuals thins considerably and the rates are less stable.

Hazard rates by FEL strata are also shown in Figure 1 for men and women separately. Again, for combined causes of death...
death, individuals from the top FEL stratum share the lowest mortality hazards, whereas those from the bottom stratum share the highest hazards. The pattern is generally the same for men and women.

Hazard rates for deaths due to heart disease are given in Figure 2. Both men and women again show the same general relationship between FEL and hazard rates established in Figure 1, where the top FEL stratum has the lowest mortality hazards at all ages. This general pattern holds for both men and women until about age 90.

Figure 3 plots cancer mortality hazard rates by FEL strata. The pattern of the relationship between FEL and cancer mortality hazards is not like the pattern for all-cause mortality hazards, nor does it conform to the main trends established for the other three age-related diseases—heart disease, stroke, and diabetes. For both men and women, there is little distinction among FEL groups in cancer mortality hazard rates until about age 80. After age 80, men in the top FEL group and women in the middle FEL group appear to have the highest hazards. The distinction among FEL groups with cancer mortality is not large, however, and underscores the lack of significant protective effect of FEL associated with cancer mortality noted in Table 2.

The difference of greater interest for cancer mortality hazards is between men and women. Overall, men have a higher lifetime cancer burden than do women, and this is evident in mortality hazards over the life span (Figure 3). Men show an earlier and faster increase in cancer mortality hazards in later life compared to women.

Figure 4 plots estimated hazard rates by FEL strata for deaths due to stroke. Here, the patterns for men and women generally conform to the all-cause pattern in which the top FEL group has the lowest mortality hazards and the bottom group has the highest hazards. Mortality hazards due to stroke are very similar over the life span for both men and women in this population.

Figure 5 plots estimated hazard rates by FEL strata for deaths due to diabetes. Mortality hazards for the top and bottom FEL strata, for both men and women, follow the predicted order very distinctly—the top longevity group has lower hazards and the bottom longevity group has higher hazards. However, for the bulk of the population in the middle FEL group, for men as well as women, rates increase earlier and more rapidly compared to those for the other groups. Diabetes hazard rates are as high for the middle and bottom FEL groups near age 80 for men and age 90 for women.

Figure 6 summarizes the age-specific hazard rates as ratios (relative risks [RR]) of top versus bottom FEL groups, for the four major causes of death and for all causes.

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<table>
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<th>Men, Age</th>
<th>All Cause</th>
<th>Heart</th>
<th>Cancer</th>
<th>Stroke</th>
<th>COPD</th>
<th>Diabetes</th>
<th>Inf/Pneu</th>
<th>Other</th>
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<td>0.0142</td>
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<td>0.0033</td>
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Notes: Three levels of FEL form groups: the top 25%, the middle 50%, and the bottom 25% of the distribution of FEL values. Rates are reported for men and women separately.

COPD = chronic obstructive pulmonary disease; inf/pneu = influenza/pneumonia.
combined. Where the ratios are low, the protective effect of being in the top 25% of the distribution of FEL is greatest. The protective benefit of FEL is greatest at younger ages, and diminishes with advancing age as the ratios approach 1. By age 90, the protective effect of high FEL is null for heart disease and stroke, persists longer for diabetes, but not beyond age 80 for cancer. Here, the weaker effect of high FEL on cancer mortality risk is evident over all ages, beginning with a higher ratio of high to low FEL from age 40.

Proportional hazard rate ratios of the middle versus bottom FEL groups (FEL\(_{m}\)) and top versus bottom FEL groups (FEL\(_{u}\)) are given in Table 4 for all causes of death; for heart disease, cancer, stroke, and diabetes; and for men and women. Birth year is also included in the model. Table 4 shows significant differences in mortality hazard rates for FEL groups, for each cause and gender. Under the proportional assumption, then, this summary measure of mortality rate differences establishes that for men, women, and each cause of death, individuals from the middle and top strata of FEL experience lower mortality rates compared to individuals at the low end of the distribution of FEL.

**DISCUSSION**

The essential result of this analysis is that familial death and familial longevity have independent effects on cause-specific mortality risks. In general, a family history of mortality due to a particular cause increases one’s risk of death from the same cause, whereas a family history of longevity has a protective effect for the same causes, except for cancer. Further analysis helped to identify in what way familial longevity might be protective against common age-related causes of death. We found that variation in FEL is associated with variation in mortality rates, so that individuals from longer lived families experience lower age-specific rates of death for the major causes—heart disease, stroke, and diabetes—but not cancer. Although the longevity effects on hazard rates, shown in Figures 1–6, are unadjusted for familial mortality (FSMR), the risk results
given in Table 2 demonstrate an FEL effect apart from that of FSMR. Therefore, we found no evidence that families with greater longevity die of causes distinct from other members of the cohort, but that they die from the same causes at reduced rates.

There are obvious limitations to using human population death records, as we have done, to help characterize phenotypes that suggest evidence of genes related to complex traits like longevity. Recorded causes of death are subject to measurement error and, inevitably, misclassifications. These likely occur on original death certificates and during conversions of old codes to newer ICD schema. We also appreciate that “primary” causes of death do not necessarily capture the single, or only relevant, disease process causing death. We narrowed our final analysis of familial longevity and mortality rate variation to four leading causes of death known to be due to age-related disease processes—heart disease, cancer, stroke, and diabetes. Although a pronouncement of death due to any of these causes is very often preceded by diagnostic morbidity experience, no ICD scheme that assigns a primary cause guarantees that there is one in any discrete sense, only that a reasonably standardized means of identification is used.

We were also concerned about misclassifications stemming from multiple code revisions enacted since 1904 and their effects over the long period of time covered by this study. Evidence of this, as well as the addition of more cases through time, is captured in a previous analysis that showed stronger FEL effects among more recent deaths (25). In any case, misclassified causes of death are not likely correlated with genealogical data in a way that would introduce familial bias, although they probably have resulted in some loss of statistical power.

We must also consider whether individuals lost to follow-up present any special challenge to a study of this type. In the UPDB population, migration out of state is the main cause of people lost to follow-up. Although they might differ in their risk characteristics from individuals with follow-up information, this difference should not enter into the relationship between familial longevity and mortality.

The overall health and longevity of the Utah population are similar in most respects to other Caucasian populations in Western Europe and North America, although Utahans consume substantially less tobacco and alcohol than do most other comparable populations, and consequently have lower overall rates of tobacco- and alcohol-related diseases (26).
is also worth noting that the Utah population is considered sufficiently representative of European gene frequencies to stand in for all Europeans in the International HapMap Project (27).

It is beyond the scope of this article to propose any particular gene associations with phenotypic variation in aging measured by familial longevity. However, some comment is warranted as to how these results fit into the emergent body of ideas regarding the genetics of aging. First, this study shows (Table 2) that familial mortality (FSMR) and familial longevity (FEL) independently affect mortality rate variation. Of particular interest from Table 2 is the significant effect of familial longevity, expressed as FEL, aside from the effects of particular family histories. Also of note is that the effect of FEL is significant for 9 of the 10 leading causes of death, and more stably in comparison to familial mortality (FSMR) for the same causes. We conclude from these trends that genetic studies of aging need not be reduce to studies of genetic predisposition to age-related diseases alone; rather, we may plausibly continue to look for genes with pleiotropic effects that are generally protective during senescence—that is, that slow aging. Examples of specific gene associations with morbidity and mortality due to these same chronic
age-related diseases abound, such as the notable one of apolipoprotein E (APOE) and heart disease (28). However, other genomic factors, such as telomere length (29) and the role of mitochondria in energy consumption and the resulting production of oxidative damage (30,31), are associated with multiple age-related diseases and various features of somatic senescence.

Although familial longevity is protective against mortality hazards for heart disease, stroke, and diabetes, it is not similarly protective with regard to cancer. The lack of an FEL effect for this disease is perhaps surprising, if only because most cancers occur relatively late in life, which leads to the general expectation that it is associated with senescence. Indeed, recent studies have identified particular genes and proteins with direct roles in tumorigenesis, as well as critical cellular functions, such as those that maintain cycling, respiration, and integration (32). Of specific interest to these studies is the link between age-related loss of tumor suppressor function and age-related decline in cell functioning. Others have proposed that cancer relates to aging as a particular example of "pleiotropy," defined as change in the fitness value of a gene in "different somatic environments" (33). In this view, the later life pattern of most cancers signals a change from beneficial gene adaptations under strong selection in early life to deleterious effects in later life, postselection (33,34). Whether tumor suppression is the critical function for this scenario is difficult to say. In general, any gene function essential to the regulation of human growth and development would likely have evolved under strong selection on earlier life traits, and have the potential to vary in fitness value with age.

Gender differences are relatively large for heart disease and cancer mortality curves (Figures 2 and 3, Table 3). As in most populations where cancer rates are reasonably monitored, men are known to have a greater lifetime burden of total cancer than are women. In Utah, prostate is the highest incident cancer, and breast is second (17). Both are highly familial over all ages, but especially among earliest age cases (before age 45), when prostate cancers are particularly rare. Men are also at higher risk of death from heart disease at all ages. Table 3 describes how later life mortality contributes to the pattern of longer life expectancy for women compared to men. However, the female life expectancy advantage is commonly established in very early life and persists throughout.

Gender differences in mortality hazard rates might indicate another form of pleiotropy due to genes with different fitness values in the somatic environments of men and women. Because men and women are unlikely to differ greatly in their exposure to alleles conferring increased disease risks, we often ascribe the consistent difference in mortality between men and women to differences in rates of aging. More generally, the differences might represent pleiotropic effects of the genetic differences that determine gender, and influence other early life patterns, such as the timing of growth, maturation, and other features of developmental health. The effects of FEL on mortality are similar across multiple categories of disease, for both women and men, and the magnitude of the difference in risk between high- and low-FEL groups for many diseases is comparable to the difference in risk between men and women. It seems reasonable, therefore, to suggest that some of the observed effects of FEL are similarly pleiotropic.

We have established familial recurrence patterns for both mortality and longevity, and have shown how familial longevity and cause-specific mortality rates are associated in this population. In addition, we advance the general notions that early- and late-life history characteristics are not fully independent and that the human aging phenotype is best thought of as an extension of the human developing phenotype. What links them, directly or indirectly, is not yet known, although recent evidence of genetic mechanisms with pleiotropic effects suggests ways in which early-life adaptations potentially bear on conditions of later life. Genes critical to cell function and regulation, and plausibly
under strong selection in early life, might also influence rates in late life, such as disease processes and mortality. Others have argued that phenotypes of the immune system are of particular interest for linking early life stages of developmental health to phenotypic aging in later life (35).

Of course, much more work is needed to bridge the considerable distance between our results as they pertain to life history traits in general, and any evidence of genetic or epigenetic mechanisms that would explain them. For instance, genetic linkage analysis of high FEL families or gene association studies that compare men and women or FEL groups have the potential to contribute greatly to our understanding of the genetics of longevity. Gene expression studies could be especially useful for identifying genes associated with phenotypic variation in early developmental stages, in late-life aging, and with mortality outcomes. The enormous gaps in our understanding of what mechanisms plausibly connect early-life phenotypes to their later life expressions, or what any phenotypic trait should look like transformed by the varying force and opportunity for selection throughout life, should inspire much future research regarding the genetics of longevity.

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REFERENCES

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