Contribution of Familial Longevity to Living to 100

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Abstract

One of the most glaring deficiencies in the current assessment of mortality risk is the lack of information concerning the impact of familial longevity. In this work, we update estimates of sibling relative risk of living to extreme ages using data from more than 1,700 sibships, and we begin to examine the trend for heritability for different birth-year cohorts. We also build a network model that can be used to compute the increased chance for exceptional longevity of a subject, conditional on his family history of longevity. The network includes familial longevity from three generations and can be used to understand the effects of paternal and maternal longevity on an individual's chance to live to an extreme age.

Introduction

The prevalence of centenarians continues to increase, due in part to dramatic and persistent decreases in infant mortality beginning in the late 1800s, increased years of education, and major improvements in socioeconomic conditions, public health and medical care that enabled average life expectancy to nearly double over the past century (Vaupel et al. 1998). As a result, many more people predisposed to achieving extreme old age have a greater opportunity to achieve these ages. What is the nature of this predisposition?

The Seventh-Day Adventist Health Study, which took place in California from 1976 to 1988, suggests that average humans can, in the setting of specific healthy behaviors (vegetarian diet, no tobacco or alcohol use, regular exercise and significant time devoted to family and religion), achieve an average life expectancy of 86 years (Fraser and Shavlik 2001). Supporting this observation, Scandinavian twin studies indicate that the vast majority of variation in survival to mid to late octogenarian years can be explained by differences in environment and behaviors (Herskind et al. 1996; McClearn et al. 1997; Iachine et al. 1998; Christensen et al. 2000; Hjelmborg et al. 2006). Heritability is generally regarded as the proportion of the variation of the expression of a phenotype controlled by genes as opposed to environmental factors (Visscher, Hill and Wray 2008). Thus, based on these twin studies, various authors and many in the lay press erroneously state that the heritability of aging and even longevity is approximately 25 percent. But more precisely, these studies and the Seventh-Day Adventist Study suggest this heritability applies to survival average people should be able to achieve in the absence of environmental factors that predispose to premature mortality and the presence of behaviors conducive to good health.

There is growing evidence, however, that heritability, or the genetic component of survival, becomes higher with survival to much older ages beyond the age of 90 (Tan et al. 2008; Gogele et al. 2010; Sebastiani et al. 2012). For example, analyses of data from about 20,000 monozygotic and dizygotic twins born in Nordic countries between 1870 and 1910 show that the genetic influence on survival is minimal prior to age 60 but increases sharply at least to the late 90s (Christensen, Johnson and Vaupel 2006; Hjelmborg et al. 2006). We have published several articles demonstrating a strong familial influence upon survival to extreme old age. Siblings of centenarians have markedly increased risk (relative risk RR = 18 for brothers and RR = 7 for sisters) of achieving age 100 relative to their birth cohort (Perls et al. 1998; Perls et al. 2002). The Okinawan Centenarian Study has also noted an increased risk of survival to extreme old age among siblings of centenarians (Willcox et al. 2006). Moreover, we noted that by their late 70s, children with at least one centenarian parent have a 60 percent reduced mortality rate compared to their birth cohort (Terry et al. 2004).

Because of our large enrolled sample of centenarians, family members and their accompanying biodemographic data, the New England Centenarian Study (NECS) (Sebastiani and Perls 2012) is in a unique position to address numerous questions about environmental and genetic factors that may contribute to living to age 100 and beyond. In this manuscript, we report updated estimates of sibling

relative risks of living to extreme longevity based on 1,384 sibships. We also measure the contribution of familial longevity to living to old ages and propose a network-based approach to examine the joint contributions of different patterns of familial longevity. The model can be used to estimate the increased odds for longevity given family history in first- and second-order relatives.

Materials and Methods

Sample. The New England Centenarian Study sample consists of approximately 2,000 centenarian probands (oldest alive in a sibship) with an age range of 95–119. Pedigree data have been obtained for more than 1,500 subjects, providing data for more than 49,000 individuals born after 1645. The pedigrees were reported from study participants, and about 250 were checked for consistency using census data, the Social Security Death Index and additional sources available through Ancestry.com. Many pedigrees have been age-validated at least for the probands and their siblings noted to survive to age ≥90. There are missing data, particularly for the subjects' grandparents and earlier generations, while data on their parents, siblings and offspring are more complete. Additional quality control and completion of the data is ongoing. Figure 1 shows an example of a pedigree that spans four generations.

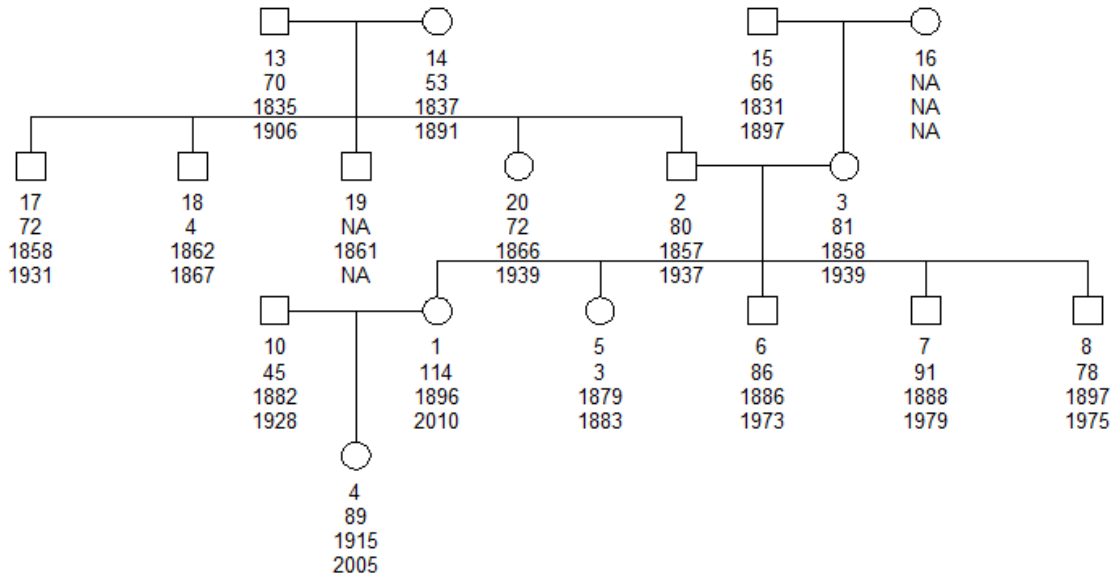

Figure 1. Example of pedigree included in the analysis. Labels under each node denote the individual identifier in the pedigree, the age at death, birth year and death year. Circles denote females and squares denote males. This pedigree includes four generations and three sibships.

Sibling relative risk. For ages A = 90, 95, 100, we estimated the sibling relative risk of living past age *A* by the ratio $\lambda(A \mid A^*) = pr(Sib > A \mid A^*) / pr(S > A \mid B, S)$, where $pr(Sib > A \mid A^*)$ is the probability that a sibling of a proband who lived past age *A** lives past age *A*, and $pr(S > A \mid B, S)$ is the probability that a subject in the population lives past age *A* (Olson and Cordell 2000). The symbols *B* and *S* denote birth year and sex. The birth-year and sex-specific probabilities $pr(S > A \mid B, S)$ were estimated using cohort life tables from the Social Security Administration (SSA) for birth-year cohorts 1900 and later (Bell and Miller 2005). For earlier birth-year cohorts, we used cohort life tables from Sweden (http://www.lifetable.de) as an

approximation of the survival experience in the United States. Eligible sibships were selected from the data based on the age of the oldest sibling, and only those sibships in which the attained age of the oldest sibling exceeded age $A^* > 90, 95, 100$ were included in the analysis. The number N of additional affected siblings in each sibship was modeled by a Poisson distribution with expected value μ that was parameterized using the log-linear model:

$$\log(\mu) = \beta_0 + \sum_k \beta_k x_k + \alpha$$

The parametric model included covariates x_k to estimate the effects of factors such as birth cohort, age at death, sex of the proband, proportion of females in the N siblings and sibship size. The parameter α denoted a random effect that modeled the correlation of sibships from the same pedigree. (For example, the pedigree in figure 1 would contribute two sibships). Bayesian estimates of the probability $pr(Sib > A \mid A^*) = pr(N = 1) = \mu e^{-\mu}$ for different sex-specific birth-year cohorts and 95 percent intervals were computed using Markov chain Monte Carlo methods in Openbugs (http://www.openbugs.info/w/). The advantage of the Bayesian analysis is that the significance of the parameters can be tested by marginalizing out the random effects, and the results typically are more robust when there is substantial correlation in the data.

Network analysis. To simultaneously analyze age at death in different generations, we recoded ages at death A of all subjects in the data set by the probability of surviving past age A, $pr(S > A \mid B, S)$, using sex and birth-year cohort-specific survival probabilities as noted above. We will refer to these probabilities as percentile survival, and the smaller the percentile survival, the more extreme the longevity. This transformation adjusts the ages at death by the trend in increasing lifespan. For example, while the percentile survival of a male born in the 1900 cohort who survived past age 95 is 1.4 percent, the percentile survival of a male born in 1850 who survived past the same age is 0.4 percent. The longest-lived individual in each sibship was selected (N = 5,497), and his/her percentile survival was used in a joint network model including these additional covariates: his/her sex, maternal and paternal ages at his/her birth, number of older and younger siblings, and percentile survival of second longest-lived sibling, of the parents, of the maternal and paternal uncles and aunts, and of the maternal and paternal grandparents. These variables were categorized into at most four categories. The percentile survival of the longest-lived subject in each sibship was categorized into four groups defined as

(1) S_1: the percentile survival was > 10^{th} using sex/birth-year matched cohort tables;
(2) S_2: the percentile survival was between 10 percent and 5 percent;
(3) S_3: the percentile survival was between 5 percent and 1 percent;
(4) S_4: the percentile survival was less than 1 percent.

Details for the other variables are shown in table A.1 in the appendix. These variables were used to generate a Bayesian classification model, shown in figure 2, which can be used to compute the posterior probability of survival into one of the four groups, S_1, S_2, S_3, S_4, based on evidence of familial longevity. The posterior probability that an individual survival is in one of the four groups S_I is given by the formula:

$$p(S = S_l \mid F_1, F_2, F_3, \ldots, F_k) = \frac{\prod_j p(F_j \mid S = S_l, \pi(F_j)) p(S = S_l)}{\sum_{i=1}^{4} \prod_j p(F_j \mid S = S_i, \pi(F_j)) p(S = S_i)}$$

where $F_1, F_2, \ldots, F_k$, are values of the covariates such as maternal age at death, paternal age at death, and number of younger or older siblings. The formula for the calculation of the posterior probability uses assumptions of conditional independence between the variables in the model that are displayed by the directed graphical model displayed in figure 2 (Sebastiani, Abad and Ramoni 2005). The node Age.P in the model represents the event where an individual's survival is in one of the four groups S_l while the other nodes are the covariates that describe different types of familial longevity. The probabilities $p(F_j \mid S = S_l, \pi(F_j))$ are estimated from the contingency tables that cross-classify each covariate, the percentile survival to one of the four groups S_l, and additional dependencies represented by the symbol $\pi(F_j)$, using standard Bayesian conjugate analysis for multinomial distributions with Dirichlet priors (Cowell et al. 1999). The additional dependencies represent known relations between the variables in the network. The advantage of this modeling approach is that the different conditional probabilities can be estimated using the largest sample size available. This approach is important here because the amount of missing data is large for some variables, particularly grandparents' generations, but much smaller for data about siblings and parents of subjects. The program Bayesware Discoverer (http://dcommon.bu.edu/xmlui/handle/2144/1288) was used to estimate the conditional probabilities and to compute the posterior probability of survival into one of the four groups. The fitted probabilities were compared against the observed ages at death to assess the goodness of fit of the model.

Results

Sibling relative risk. We generated estimates for sibling relative risk using 1,714 sibships obtained from 1,505 NECS pedigrees in which the oldest sibling attained an age of at least 90 years, and the age range was 90–116. We used Poisson regression with a log-linear model of the mean to estimate the probability that one additional sibling in each sibship lived past age A, given that the longest-lived sibling reached age A*, as detailed in methods. Covariates in the regression model included the age at death of the proband, sex and birth-year cohort coded as a binary variable (1895–1905 or <1895). We repeated the analysis for probands who lived past ages A* = 90, 95 and 100.

			2nd sib A = 90+		2nd sib A = 95+		2nd sib A = 100+
Probands	**Sex**	**90+**	**95+**	**100+**	**95+**	**100+**	**100+**
1895–1905	M	2.11	2.74	3.35	3.98	5.49	8.21
	F	2.32	2.95	3.52	4.23	5.79	12.42
Before 1895	M	4.88	6.39	7.95	18.16	24.80	//
	F	5.36	6.92	8.43	19.29	26.15	//

Table 1. Estimates of relative risk that a male or female sibling lives past age A, given that the proband lived past age 90, 95 and 100, respectively, and was born between 1895 and 1905 (row 1/2) or before 1895 (row 3/4). Data were insufficient to estimate risk in cases of probands born before 1895 who lived past age 100.

Results in table 1 show that sibling relative risk increases with increasing ages of the proband, increasing age of the sibling and earlier birth-year cohort of the probands. For example, male siblings of centenarians born in the 1900 birth-year cohort had a 3.08 times greater chance of living past age 90, compared to people born in the 1900 birth-year cohort, and 9.41 times greater chance of living past age 100. Pedigrees of centenarians enrolled for a sib-pair genetic linkage study (Geesaman et al. 2003) were not included in this analysis. The estimates agree with sibling relative risks for nonagenarians reported from Utah (Kerber et al. 2001) and Iceland studies of longevity (Gudmundsson et al. 2000), and show that the risk increases noticeably for ages 100 and older. The estimates of sibling relative risks for the 1900 birth-year cohort of the probands are smaller than results previously published (Perls et al. 2002), but those results pulled together a wider range of birth-year cohorts that are associated with larger risks.

Network analysis. Figure 2 displays the network implemented in the program Bayesware Discoverer. Twenty-seven percent of the sibships in the NECS study had the longest-lived individual surviving past the top 1 percent survival, and, in 13 percent of the sibships, the percentile survival of the longest-lived individual was between 5 percent and 1 percent. Therefore, the contribution of different types of familial longevity needs to be compared to these prior probabilities.

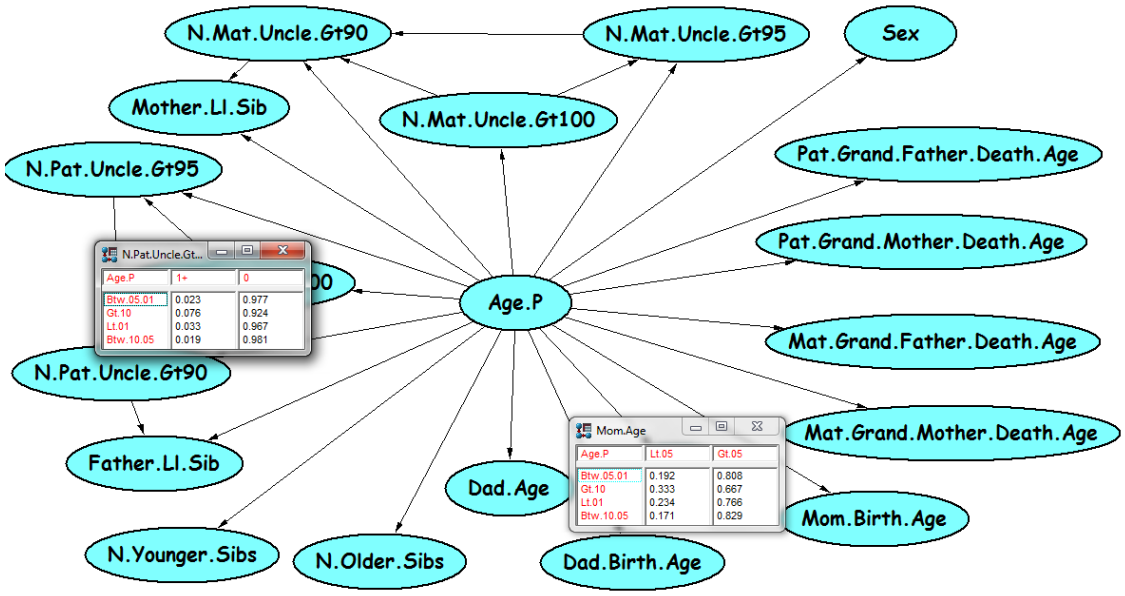

Figure 2. Display of the Bayesian classification model used to estimate the contribution of familial longevity of an individual's chance for extreme survival.

Some selected vignettes from the results of the network model include the following findings. NECS subjects who survived past the fifth percentile survival were more likely to be female and to have some type of familial longevity. For example, the odds that the father survived past the fifth percentile survival increased by 1.13, while the odds of an uncle/aunt surviving past the 10^{th} percentile survival increased by 1.34 relative to NECS subjects who did not survive past the fifth percentile. Those who survived past the fifth percentile survival were also more likely to be from larger families with several siblings. Analysis of the network showed that paternal longevity contributes to an individual's longevity more than maternal longevity, and the odds that an individual survives past the top 1 percent survival increases by 15 percent

if the father lived past the 5 percent survival of his birth-year cohort. Having maternal or paternal uncles and aunts who survived past the 10 percent survival increases the odds for longevity by 1.5, and additional family history of longevity (for example, one of the paternal grandparents surviving past the 10th percentile) also contributes to an increase in the odds for an individual's longevity. Ages of parents at a subject's birth have an effect that changes with the number of siblings: being born from older parents seems to have a detrimental effect on an individual's longevity in small sibships but not in large sibships.

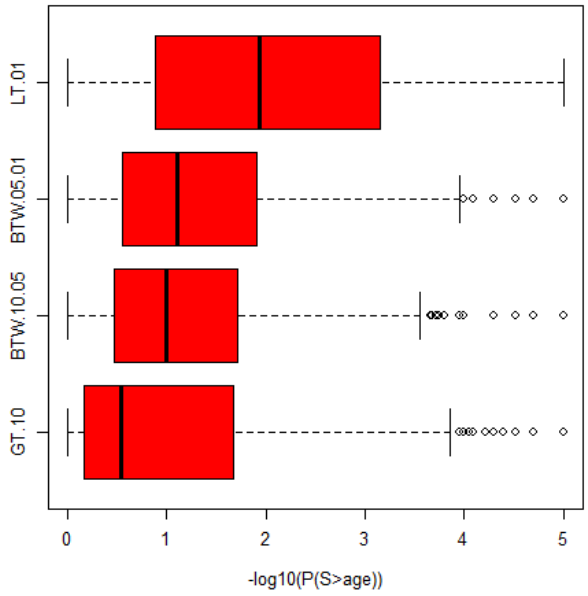

Figure 3. Boxplots of -log10 (percentile survival) in the four groups predicted by the Bayesian model based on the largest posterior probability. The four groups are: GT.10: if the age at death of a person is >10th percentile survival; BTW.10.05: if the age at death is between the 10th and the fifth percentile survival; BTW.05.01: if the age at death is between the fifth and the first percentile survival; and LT.01 if the age at death is older than the first percentile survival. The four boxplots show that subjects allocated to the group with the most extreme survival reached extreme percentile survival. For example, the median percentile survival for subjects classified as GT.10 was 28 percent, while the median percentile survival for subjects allocated to group LT.01 was 0.1 percent.

Although the results are preliminary, they suggest that a history of familial longevity contributes to increasing the odds for an individual's longevity, and that the different components of familial longevity can be combined to estimate an individual's odds for living to extreme ages. Initial validation of the probability computed with the network model is positive (see figure 3). However, additional validation of the model using independent data is needed. When the model was used to classify the subjects of the study into the most likely groups of survival based on the predicted probabilities and assuming uniform prior probabilities, 41 percent of subjects were correctly classified, which is more than 1.4 times the rate expected by a random classification.

Conclusions

Analysis of this large number of sibships from families of centenarians in the New England Centenarian Study validated previous estimates of the sibling relative risk of living past extreme ages. The increasing relative risks of survival to very old age that is associated with older and older ages of the relative is consistent with the conjecture that the heritability of longevity is substantial only when we start looking at the oldest fifth and smaller percentiles of survival. In addition, we used network modeling to begin combining different contributions of familial longevity into a single risk measure. As we obtain more complete pedigree data, we anticipate conducting more sophisticated network analyses and possibly more accurate models will be generated.

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Node name	Categories	Description
AGE.P (longevity score)	GT.10	age at death < age at which 10% of sex, birth year matched cohort survived
	BTW.10.05	age at death between ages at which 10% to 5% of sex, birth year matched cohort survived
	BTW.05.01	age at death between age at which 5% to 1% of sex, birth year matched cohort survived
	LT.01	age at death > age at which 1% of sex, birth year matched cohort survived
Mom.age Score maternal age at death	GT.05	age at death < age at which 5% of female, birth year matched cohort survived
	LT.05	age at death ≥ age at which 5% of female, birth year matched cohort survived
Dad.age Score paternal age at death	GT.05	age at death < age at which 5% of males, birth year matched cohort survived
	LT.05	age at death ≥ age at which 5% of male, birth year matched cohort survived
Mat.Grand.Mother.Death.Age Score of age at death	GT.10	age at death < age at which 10% of female, birth year matched cohort survived
	LT.10	age at death ≥ age at which 10% of female, birth year matched cohort survived
Mat.Grand.Father.Death.Age Score age at death	GT.10	age at death < age at which 10% of male, birth year matched cohort survived
	LT.10	age at death ≥ age at which 10% of male, birth year matched cohort survived
Pat.Grand.Mother.Death.Age Score age at death	GT.10	age at death < age at which 10% of female, birth year matched cohort survived
	LT.10	age at death ≥ age at which 10% of female, birth year matched cohort survived
Pat.Grand.Father.Death.Age Score age at death	GT.10	age at death < age at which 10% of male, birth year matched cohort survived
	LT.10	age at death ≥ age at which 10% of male, birth year matched cohort survived
N.Mat.Uncle.GT.100	0	number of maternal uncles/aunts who lived past the age at which 1% of sex, birth year cohort survived
	1 or more	
N.Mat.Uncle.GT95	0	number of maternal uncles/aunts who lived past the age at which 5% of sex, birth year cohort survived
	1 or more	
N.Mat.Uncle.GT90	0	number of maternal uncles/aunts who lived past the age at which 10% of sex, birth year cohort survived
	1 or more	

N.Pat.Uncle.GT100	0 1 or more	number of paternal uncles/aunts who lived past the age at which 1% of sex, birth year cohort survived
N.Pat.Uncle.GT95	0 1 or more	number of paternal uncles/aunts who lived past the age at which 5% of sex, birth year cohort survived
N.Pat.Uncle.GT90	0 1 or more	number of paternal uncles/aunts who lived past the age at which 10% of sex, birth year cohort survived
FATHER.LL.SIB longevity score of oldest paternal uncle/aunt	GT.10 LT.10	longest lived sib age at death < age at which 10% of sex, birth year matched cohort survived longest lived sib age at death > age at which 10% of sex, birth year matched cohort survived
MOTHER.LL.SIB longevity score of oldest maternal uncle/aunt	GT.10 LT.10	longest lived sib age at death < age at which 10% of sex, birth year matched cohort survived longest lived sib age at death > age at which 10% of sex, birth year matched cohort survived
Mom.birth.age maternal age at birth of subject (years)	< 30 between 30 and 35 35 and older	
Dad.birth.age paternal age at birth of subject (years)	< 30 between 30 and 40 40 and older	