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Familial Excess Longevity in Utah Genealogies

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We evaluated the influence of family history on longevity by examining longevity in a cohort of 78,994 individuals drawn from the Utah Population Database (UPDB) who were born between 1870 and 1907, and lived to at least age 65. We examined Mendelian genetic and social modes of transmission of excess longevity (the difference between observed and expected longevity) by varying weighted kinship contributions over different classes of relatives. The genetic component of the variation in excess longevity measured as heritability, h^2, was approximately 0.15 (95% confidence interval [CI] 0.12–0.18). Among siblings of probands who reached the 97th percentile of excess longevity (+14.8 years, currently age 95 for men and 97 for women), the relative risk of recurrence (λ_s) was 2.30 (95% CI 2.08–2.56). In sibships whose relatives were in the top 15% of the distribution for familial excess longevity, the value of λ_s increased substantially, indicating that considering the longevity of distant relatives may be helpful in the selection of families in which to identify genes influencing aging and longevity.

THE identification and characterization of familial patterns of longevity in humans is a critical first step in the identification and characterization of genes that affect longevity. If family linkage studies of longevity are to prove successful, there must be a reasonably high probability that longevity will recur in the relatives of a long-lived individual. Moreover, the variability of recurrence rates among different classes of relatives contains important information about modes of inheritance, as Risch (1) and many others have shown. To date, most studies of the familiality of longevity have focused on siblings or other close relatives. Our study goal was to extend our understanding of the characteristics of familial longevity by using a variety of techniques to explore patterns of familial aggregation of longevity in a large population-based genealogical database.

In humans, the familial component of age at death has been examined repeatedly over the last century by biologists, population geneticists, evolutionists, and demographers (2–12). Reported heritability estimates of age at death vary widely, ranging from nearly zero (6) to 0.33 (13), in part because of differences in the types of paired relationships examined, the time periods and number of generations considered, and the quality of data among source populations. These estimates are normally derived from familial correlations; as such, they are always elevated by nongenetic factors shared by families, but that vary within and between populations.

Previous studies of familial correlations in the duration of life using Utah genealogies were limited to examining parent–offspring and sibling–sibling correlations in families containing twins (8,11). Here, we present a more comprehensive study, using life-span data on all relatives of a cohort of individuals born between 1870 and 1907, who lived to at least age 65, and who were selected on the basis of having complete vital status follow-up data. We used a combination of linear regression and parametric survival models to evaluate the impact of familial survival on individual survival. For comparison with earlier reports on the familial component of longevity in this and other populations, we also used traditional methods to estimate the heritability of excess longevity based on sibling–sibling, parent–offspring, and spouse–spouse correlations.

In this report we begin to address the problem of selecting living sibships in which to identify genes contributing to slower aging. Recently developed genetic linkage analysis methods using carefully selected sibling (sib) pairs may simplify the problem of mapping quantitative trait loci (QTLs; 1,14–16). The power to detect linkage using sib pairs depends on the magnitude of the relative risk to siblings of exceeding some extreme level of the trait, given that a proband sibling also exceeds that trait level. Using sib pairs drawn from our subject cohort, we have calculated recurrence risks for extreme longevity in the Utah Population Database (UPDB).

METHODS

The Utah Population Database

The UPDB consists of genealogical records originally obtained from the Utah Family History Library, linked to birth and death records contributed by the Utah Department of Health, and other data of biomedical relevance (17). The genealogical records have been linked to Utah death certificates for the years 1934–1996 using probabilistic record linkage methods (18). About 60% of Utah death certificates for these years can be linked to extant genealogical data. UPDB currently describes more than two million individuals born between 1800 and 1998, with an average pedigree depth of about four generations (19).

Maintenance and update of a large population database is an ongoing process. At any point in time, many individuals

in UPDB with known genealogical origin lack complete vital status information. It is in the context of new and ongoing studies based on UPDB that new data sources are linked to it and provide updates or previously missing information. For example, approximately 10% of individuals born between 1850 and 1880 had no known death date. Almost 17% of those born between 1881 and 1900 lacked death dates, although only a small fraction of these could be living. Therefore, we linked 240,000 UPDB records of individuals born between 1852 and 1931 for whom vital data were incomplete, to the vital status file of the Health Care Financing Administration (HCFA). We observed that the vital status data we received began around 1972. If 120 years is the current maximum human life span, we need not have searched for HCFA records for individuals born prior to 1852. Because HCFA data are not routinely available for individuals under the age of 65, data were not available in January 1997 (when the record linking was done) for people born after 1931. A total of 139,061 of the UPDB records matched HCFA records, allowing us to update the records of 96,812 living individuals and the more recently deceased status of 42,249 individuals. No one born before 1870 was positively linked to a HCFA record.

Using the combined UPDB–HCFA data, we identified a cohort of 243,773 people born between 1870 and 1931 for whom we had vital status follow-up in the form of either a UPDB death record (from the genealogical data or death certificates) or a HCFA vital status record. Of these, 78,994 were born from 1870 through 1907 (the last year during which one could have been born and be followed during the interval 1972–1996) and lived at least 65 years. These records formed the basis of our analysis. The Institutional Review Board of the University of Utah has approved this study.

Definition of Longevity

It is difficult to establish a definition of longevity that highlights only the attributes that are of interest for a particular application. Numerous factors that are unrelated to genetic predisposition to longevity are nonetheless related to observed individual life span. Among these factors are gender, birth cohort, exposure to infectious disease, variability in social support, and behavioral factors such as smoking. Infectious disease, social, and many behavioral factors have substantial familial components and may mislead an assessment of familial longevity due to genetic contributions.

Our approach to minimizing the influence of these potential confounding factors is to choose as an outcome variable excess longevity, defined as the difference between an individual's attained age and the age to which that individual was expected to live according to a model that incorporates the potential confounders.

The expected longevity ($\hat{y}$) can be conveniently estimated from an accelerated failure time model in the following manner:

$$\hat{y} = e^{\alpha + \beta_1 \cdot gender + \beta_2 \cdot birthyear + \ldots},$$

where α is the intercept, $\beta_1 \ldots \beta_n$ are slope coefficients, and the excess longevity (l) is simply, $y–\hat{y}$, where y is the attained age in years. The excess longevity approach, as we have defined it, is similar to the method applied by Bocquet-Appel (20) in estimating the heritability of longevity at Arthez d'Asson.

We have chosen to estimate $\hat{y}$ and l using only individuals who survived to at least age 65 for two reasons. First, we are presently unable to confirm that individuals for whom we have no death dates are alive at ages less than 65, because we rely on HCFA records for follow-up of living individuals. The inclusion of individuals for whom no follow-up data are available can produce spurious familial aggregations of mortality or morbidity, because loss to follow-up aggregates in families. The second reason we have excluded individuals younger than 65 from analysis is that we are interested in reducing the impact on our analyses of familial aggregation of mortality that results from predisposition to particular diseases, such as heart disease, cancer, or diabetes. Although individuals for whom we cannot confirm vital status or survival past the age of 65 were not included directly in the calculation of excess longevity or familial excess longevity, they were not omitted from the data set, because they were needed to establish the genealogical connections between individuals for whom longevity could be estimated.

Familial Excess Longevity

The concept of excess longevity can be extended to the family members of each subject, excluding those who did not live at least 65 years. Averaging the excess longevities of all of a subject's family members, with an appropriate weighting scheme, yields an estimate of the familial excess longevity. For the present analysis, we have chosen two primary weighting schemes, each corresponding to a different model of transmission of familial longevity. The kinship coefficient, the probability that an individual shares a single nuclear gene with another individual, is used as a weight in calculating Mendelian excess longevity (21):

$$ml_i = \frac{\sum_{k \varepsilon K} f(i,k) \cdot l_k}{\sum_k f(i,k)},$$

where ml_i is the Mendelian excess longevity for subject i, K is the set of all relatives of subject i, l_k is the excess longevity of the kth member of K, and $f(i,k)$ is the kinship coefficient (22), the probability that i and k share a given gene identical by descent from a common ancestor. To assess the impact that familial but nongenetic factors have on longevity, we constructed an index of social excess longevity, which is the average excess longevity among the spouses of a subject's relatives, weighted by the kinship coefficient of the subject and the relative:

$$sl_i = \frac{\sum_{s \varepsilon S} f(i,k_s) \cdot l_s}{\sum_s f(i,k_s)},$$

where the set S is the set of spouses of the members of the previously defined set K, and k_s is the corresponding rela-

Table 1. Characteristics of the Baseline Data Set

Birth Year and Characteristics	UPDB Total*	Followed†		65+‡	
		n	Percent	*n*	Percent
<1870	130,909	116,092	88.7	59,779	45.7
1870–1879	63,218	57,137	90.4	28,140	44.5
1880–1889	81,578	69,669	85.4	35,699	43.8
1890–1899	92,932	76,692	82.5	42,618	45.9
1900–1907	82,270	66,927	81.4	41,419	50.3
Male	230,030	199,826	86.9	103,146	44.8
Female	220,877	186,691	84.5	104,509	47.3
LDS	176,962	159,357	90.1	113,699	64.3
Not LDS	273,945	227,160	82.9	93,956	34.3
Total	450,907	386,517	85.7	207,655	46.1

Note: UPDB = Utah Population Database; LDS = affiliated with Church of Jesus Christ of Latter-day Saints.

*Total individuals in UPDB genealogy born between 1870 and 1907.

†Total individuals in UPDB genealogy born 1870–1907, with either a death date or HCFA follow-up.

‡Total individuals in UPDB genealogy born 1870–1907, with follow-up data, who lived at least 65 years.

tive (the spouse of *s*). If k_s has more than one spouse, only the first is used. In the presence of assortative mating, adjusting for *sl* may result in a biased estimate of the effects of *ml* on longevity. Assortative mating for longevity might seem unlikely, but if factors that stratify the population in some social terms also stratify the population genetically (e.g., the country of origin of one's ancestors), such effects are possible.

Baseline Survival Analysis

The data set for baseline survival analysis consisted of all individuals in UPDB who were born before January 1, 1908, who had follow-up data in the form of a death date or a HCFA vital status record, and who lived to at least age 65. There were 207,655 such individuals, representing about half (48.1%) of the individuals born prior to 1908, or 56.1% of those for whom follow-up data were available. Table 1 shows the proportions of individuals by cohort, sex, and religious affiliation who made up the baseline data set. Religious affiliation was measured indirectly, by observing whether an individual had been "endowed" by the age of 40. Endowment is a personal pledge that signifies a deep commitment to the Church of Jesus Christ of Latter-day Saints (LDS) church and represents a strong religious attachment to the church. Endowment dates are recorded among the genealogical data in UPDB. There are only minimal differences in the proportions followed by sex or religious affiliation, and a moderate drop (from about 90% to about 80%) in the proportion followed as birth cohorts become more recent. The proportions of people reaching age 65 do not differ appreciably by sex or birth cohort. Individuals known to be affiliated with the LDS church were about 1.9 times as likely to reach age 65 as non-LDS individuals. One reason for this is that those who died at young ages (less than 40 years old) could not be classified as LDS. There may also be substantive reasons for this difference in survival, however. Because consumption of tobacco and alcohol is very infrequent

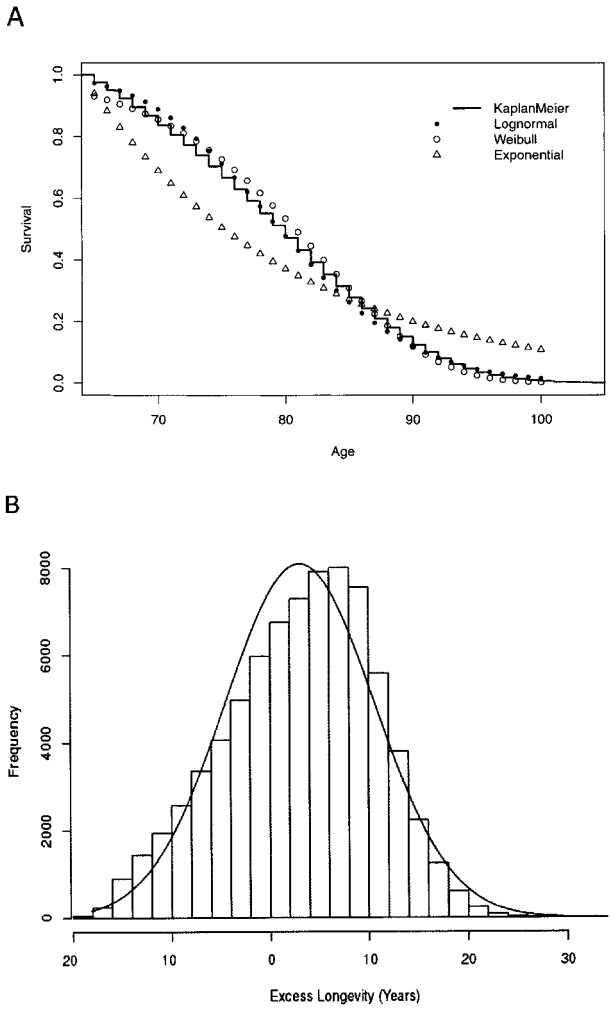

Figure 1. **A**. Fit of various parametric models of baseline survival at age 65 for members of the UPDB population. **B**. Distribution of excess longevity among members of the cohort.

in the LDS population of Utah, affiliation with the church is likely to reduce the risk of death from birth to age 65. Other factors, such as socioeconomic factors, family support, and genetic differences, might also conceivably play a role in the greater longevity of the LDS population.

Table 2. Baseline Model for Excess Longevity

Covariate	Beta§	*SE*‖	*p*¶	Years**	95% CI††
Female*	.0313	.00046	<.0001	2.55	2.48–2.63
Birth year†	.0007	.00001	<.0001	0.05	0.046–0.054
LDS‡	.0159	.00052	<.0001	1.29	1.20–1.37

*Effect of being female (compared to male).

†Year of birth (as a continuous variable).

‡Affiliation with Church of Jesus Christ of Latter-day Saints.

§Beta = slope of regression model.

‖*SE* = standard error of regression estimate.

¶Probability under null hypothesis.

**Change in life expectancy associated with a unit change in covariate.

††95% confidence interval around estimated change in life expectancy.

Only a limited set of potential covariates was available for the baseline analysis: sex, year of birth, and religious affiliation. Expected life spans ($\hat{y}$) used in the estimation of excess longevity and familial excess longevity were calculated using parametric (accelerated failure time) survival analysis methods (23). Parametric methods require that the distribution of failure times be specified prior to fitting the model. We compared the fits of models based on the lognormal, Weibull, log-logistic, and exponential distributions with the observed survival of the baseline data, as summarized by Kaplan-Meier (nonparametric maximum likelihood) estimates of survival probabilities (24). Figure 1A shows the fit of several models. The lognormal and log-logistic models appeared to provide the best fit for the observed data (the log-logistic model is not shown in Figure 1A—its fit is virtually identical to that of the lognormal model); a Weibull distribution also fit the observed data quite well. The exponential distribution is clearly inappropriate for the observed data. Coefficient estimates were similar in all models.

We used the lognormal model to estimate excess longevity and familial excess longevity among members of the cohort. All the available covariates—female gender, year of birth, and religious affiliation—were significantly related to survival past age 65 in the baseline data set. Table 2 lists the slope coefficients (β), standard errors, confidence intervals (CI), and p values from the lognormal model of survival past age 65 among members of the baseline data set. The "Years" column in Table 2 shows the difference in expected life span given a unit change in the corresponding covariate in comparison to an LDS male born in 1900; 95% CIs around the estimated change in life span are also given. Affiliation with the LDS church is associated with better survival past the age of 65. This is likely to be due, at least in part, to the fact that members of the LDS church rarely use tobacco or alcohol. Our subsequent analyses are adjusted for all the baseline covariates given in Table 2.

Regression Methods

Multiple linear regression methods were used to evaluate the relationship between excess longevity in cohort members and familial excess longevity using each of the two weighting schemes described above. The statistical package R (25) was used for all regression analyses. The software package BUGS (26) was used for the Gibbs sampling analyses (see below).

Adjustment for measurement and sampling error.—Each of our indices of familial excess longevity has an associated variance estimate, which is dependent on both the variability of longevity among the relatives of a subject and the number of relatives for whom follow-up data were available. Thus, familial excess longevity in UPDB is measured with error, and we can estimate the standard error of our excess longevity estimates from our primary data. It is well known that the use of covariates that have been measured with error in regression models results in a bias toward the null. It is less well known that the inclusion of several such variables in a multiple regression model can produce overestimates as well as underestimates of the effects of interest (27).

Because we were interested in adjusting for the effects of social as well as biological transmission of longevity, we chose an approach based on Gibbs sampling (27) to correct for the measurement error in our data. Briefly, Gibbs sampling is an approach to Markov chain Monte Carlo modeling, in which possible parameter values are repeatedly generated from a defined set of prior distributions; the proposed values are accepted or rejected according to a conditional likelihood defined by the model. After a "burn-in" period during which the parameter estimates converge, the observed distribution of the accepted parameter values can be used to make inferences about the true joint distribution of the parameters.

We assumed that the estimated values of familial excess longevity were normally distributed around the (unknown) true values for familial excess longevity, with variance equal to the square of the estimated standard errors. The excess longevity estimated for an individual was then modeled as a linear function of the individual's sex and birth year (both assumed to be measured without error) and the unknown true values for Mendelian and social excess longevity, as follows:

$$l = \alpha + \beta_1 \cdot gender + \beta_2 \cdot birthyear + \beta_3 \cdot tml + \beta_4 \cdot tsl + \varepsilon,$$

where l is the individual's excess longevity (as defined above); α is the intercept; $\beta_1 \ldots \beta_4$ are slope coefficients for, respectively, birth year, gender (0 for male, 1 for female), *tml* (the true Mendelian excess longevity), and *tsl* (the true social excess longevity), and ε represents the error in the fit of the model.

Familial Correlations and Heritability Estimates

For comparison with other reports in the literature, we calculated heritability (h^2) estimates using methods derived from those of Rao and colleagues (28), and transmissibility (t^2) estimates using the methods of Rice and coworkers (29). Sib–sib correlation coefficients for excess longevity are given for pairs of sibs chosen at random from each nuclear family with at least two sibs born no later than 1907 and who survived to age 65 (or greater); there were 42,812 such families. Parent–offspring correlations are given for one child chosen at random from the sib pair sample for those families with follow-up data on both parents; there were 19,575 such families. The same strategy was used to identify grandparent–grandchild pairs (n = 25,903), aunt/uncle–niece/nephew pairs (n = 29,512), and first cousin pairs (n = 29,305). In addition, we identified all pairs of same-sex (n = 472) and opposite-sex twins (n = 238) meeting our inclusion criteria and random pairs of maternal half-sibs (n = 3,398).

Rao and associates (28) identify through path modeling a set of coefficients that, in principle, can be estimated from a set of familial correlations. Because we do not have direct data on shared environments, we cannot estimate the full set of parameters from our data. In particular, it is tempting to treat maternal half-sibs as "half-sibs reared together" (as we

have done) and paternal half-sibs as "half-sibs reared apart," but because many of the paternal half-sibs in our data were raised in polygamous households (which may occupy some intermediate state between "reared together" and "reared apart"), we have not tried to exploit this particular contrast. We have estimated the parameters *c* (effect of common environment), *r* (correlation of midparent genotype with common environment), and *h* (effect of genotype on child's phenotype) from the Rao model.

The "unitary" model of Rice and colleagues (29), which was employed by Bocquet-Appel (20), does not estimate h^2 directly. Rather, the unitary model allows the estimation of the total transmissibility (t^2) of a trait, including both genetic and cultural transmission. The model does allow, however, for testing of the hypothesis that there is no cultural transmission.

Determination of Relative Risk

Relative risks of recurrence in multiple classes of relatives (λ_r, where *r* is one of: parents, siblings, aunts and uncles, first cousins, first cousins once removed, or second cousins) were calculated for purposes of fitting several models of single-locus and multiple-locus inheritance described by Risch (1). Values of λ_r were estimated using the method of Bai and colleagues (30), using all members of the cohort who had surpassed the 99th percentile of the excess longevity distribution as cases, and 5,000 random individuals from the cohort who did not exceed the 97th percentile of excess longevity as controls. The number of controls was selected arbitrarily to provide reasonable precision while not producing overwhelming numbers of relatives. Bai and colleagues note that recurrence risk estimates will be biased by the usual practice of selectively omitting members of families that have been previously selected as either "case" or "control" families. Unbiased estimates of recurrence risk result from including all kin of a given class in the analysis, even if those same individuals are tabulated multiple times (either as relatives of cases, or controls, or both). Although relative risk estimates calculated by this method are unbiased, the variance of such estimates has not been described. We therefore report bootstrap estimates (31) for the variance and confidence intervals for λ_r.

We fit several models of inheritance to the observed values of λ_r, following the approach used by Risch (1). Model I is a single-locus model (which, however, cannot be distinguished from the additive effects of multiple loci), in which the excess relative risk ($\lambda_r - 1$) is halved with increasing degree of relationship. Model II assumes an infinite (or very large) number of loci with small individual effects, in which the relative risk decreases by a power of .50 with each additional degree of relationship. Model III includes both a single major locus and an infinite number of loci of small effect; therefore the fits of Models I and II can be compared to the fit of the more general Model III. We estimated values for relative risks under each model by maximum likelihood, assuming the observed values of λ_r were normally distributed around the predicted values with variance given by the bootstrap estimator.

The relative risk to siblings, λ_s, was also calculated at a variety of other cutpoints using the method described above. We repeatedly calculated the recurrence risk of extreme longevity in the siblings of "proband" subjects with excess longevity greater than or equal to each percentile of the distribution from 85% to 99% in 2% intervals, relative to siblings of subjects whose excess longevity was less than that of the probands. This is a variant of the method proposed by Gu and Rao (15). Because in the actual conduct of a sib-pair study one will encounter pairs of sibs with differing ages (and differing excess longevities), we estimated the relative risk for each percentile of proband (*x*) and sib (*y*) longevity,

$$\lambda_{s[x,y]} = P(l_1 \geq x \,|\, l_2 \geq y) / P(l \geq x),$$

where l_1 and l_2 are the excess longevity of the proband and sib, respectively. The method of Bai and colleagues (30) assigns "proband" status to both members of a sib pair, so it is reasonable to assume that $\lambda_{s[x,y]} = \lambda_{s[y,x]}$, and that departures from symmetry are the result of measurement error. We thus estimated the $\lambda_{s[x,y]}$ for $x \neq y$ as $(\lambda_{s[x,y]} + \lambda_{s[y,x]})/2$.

In order to determine whether the addition of information on more distant relatives usefully increased the estimate of λ_s, we selected all those sibships from our random sample for whom the estimated Mendelian excess longevity among all family members except siblings was greater than the 85th percentile of the distribution of Mendelian excess longevity in the population (approximately 2.3 years). We estimated λ_s among this subgroup in the manner described above.

Results

Figure 1B shows the distribution of excess longevity among the 78,994 subjects in the UPDB–HCFA cohort. Note that the distribution of excess longevity among cohort subjects is not centered on zero. This is because cohort members were alive in 1972, regardless of year of birth, so cohort members born in every year prior to 1906 had to be more than 65 years old at follow-up. Although the distribution is fairly close to a normal distribution, it is somewhat skewed. This is probably due to mixing observations on deceased subjects (with death dates) and living subjects (with censored death dates), because the distribution appears increasingly normal for earlier cohort birth years (data not shown). A total of 7,997 subjects (10.1% of the cohort) were still alive at the time the HCFA records were linked in 1997. The median family size among members of the cohort was 1,987 (with a range from 2 to 41,824); the mean family size was 3,112. The median total kinship with followed biological relatives (the denominator for ml_i) among members of the cohort was 4.5 (range 0.5–28.3), with a mean of 5.0.

Table 3A shows the relationship of both of our indices of familial excess longevity to individual excess longevity among cohort members, as estimated by a multiple linear regression model simultaneously incorporating each of the indices. A strongly significant Mendelian effect (*ml*) is apparent in the data, about 5 months of excess longevity (0.41×12 months) for every excess year of survival of a subject's relatives. Individual excess longevity, as we have measured it, already takes into account variation resulting from one major social factor: the subject's LDS church affiliation. The very small effects associated with social excess longevity (*sl*) independent of effects associated with church affiliation

Table 3. Multiple Linear Regression: Effects of Familial Excess Longevity on Excess Longevity

Weighting*	Slope (years)	*SE*	95% CI
A. Unstandardized Linear Regression Model			
Mendelian†	0.41	0.012	0.39–0.43
Social‡	–0.002	0.011	–0.02–0.02
B. Standardized Linear Regression Model			
Mendelian	0.123	0.0036	0.12–0.13
Social	–0.0005	0.0036	–0.01–0.01
C. Standardized Regression Model Adjusted for Measurement Errors§			
Mendelian	0.122	0.0031	0.12–0.13
Social	–0.0008	0.0036	–0.01–0.01

*Weighting scheme used to calculate familial excess longevity.
†Mendelian = all relatives included, kinship weights.
‡Social = spouses of biological relatives, weighted by kinship to relative.
§Adjusted via Gibbs sampling (see text).

suggest that little residual variation is patterned along family lines, after the baseline model has been fit to the data.

The slope estimates given in Table 3A are interpretable in terms of years of excess longevity per year of familial excess longevity, but the slope estimates for *ml* and *sl* cannot be easily compared to one another because the variance of *sl* is greater than that of *ml*. In order to facilitate direct comparison of the magnitude of Mendelian and social effects, we standardized the excess longevity measurements by transforming them into standard normal deviates (by subtracting the mean and dividing by the standard deviation of each measurement). The results of the regression analysis of standardized excess longevity (given in Table 3B) can be used to directly compare the strength of the Mendelian effect with any residual social effect. In Table 3B, the residual social effect appears to be essentially nil. Adjusting for the measurement error via Gibbs sampling has very little impact on the slope estimates for either Mendelian or social excess longevity (Table 3C).

Table 4 gives the familial correlation and crude heritability results. All the correlation coefficients are significantly different from zero. The estimated value of h^2 from the Rao model is 0.147, nearly the same as the crude h^2 of 0.149 obtained by doubling the parent–offspring correlation. The estimate of t^2 from the Rice model (0.168) is approximately equal to the sum of h^2 and c^2 from the Rao model (0.175). It is apparent from the comparison of expected to observed values in Table 4 that a substantial residual association of like-sex and like-generation individuals persists despite the use of excess longevity as an outcome variable. For example, the like-sex twins are correlated at a level beyond the expected value, and the opposite-sex twins are less correlated than expected. First cousins are more correlated than expected, while parent–offspring and grandparent–grandchild pairs are less correlated than expected. These patterns suggest that the estimates of heritability given in Table 4 should be viewed with some caution, although the inclusion of a large and varied set of kin comparisons should increase the robustness of the estimates. It is also worth noting that the parameter *m* from the Rice model is a direct estimate of the effect of assortative mating. Our estimate of this parameter is nearly zero, suggesting that the influence of assortative mating on these data is minimal. We also calculated Spearman's rank correlation for parent–offspring and sib–sib correlations, in order to evaluate the sensitivity of heritability estimates to the normality assumptions implicit in both the regression and correlation analysis. For both comparisons, the Spearman correlation was within 1% of the Pearson correlation, indicating that the normality assumption did not have an important influence on these results.

Table 5 shows rates of recurrence and relative risks of recurrence (λ_r) of excess longevity greater than or equal to the 99th percentile for various classes of relatives. Bootstrap confidence intervals are given for each estimate of λ_r. Also shown in Table 5 are the predicted values of λ_r from Risch's

Table 4. Familial Correlations and Heritability of Excess Longevity for Pairs of Individuals Surviving at Least 65 Years, One Random Pair per Family

			Rao Model*		Rice Model†	
Correlation	Pairs	Observed	Formula	Expected	Formula	Expected
Like-sex twins	472	0.249	$c^2 - g^2 + 2 + (h^2 + grc) + \frac{g^2 - h^2}{1 - P}$	0.136	—	—
Opposite-sex twins	238	0.078	$c^2 + g^2 + 2\,grc$	0.102	—	—
Sib–Sib	42,812	0.107	$c^2 + g^2 + 2\,grc$	0.102	$2\tau^2(1 + mt^2)t^2$	0.086
Parent–Offspring	19,575	0.074	$c^2 + g^2 + 2\,grc$	0.102	$\tau(1 + m)t^2$	0.086
Maternal half-sib	3,398	0.101	$c^2 + \frac{1}{2}g^2 + 2grc$	0.065	—	—
Grandparent–Grandchild	25,903	0.015	—	—	$\tau^2(1 + m)(1 + mt^2)t^2$	0.044
Aunt/Uncle–Niece/Nephew	29,512	0.021	—	—	$2\tau^3(1 + mt^2)^2t^2$	0.044
First cousins	29,305	0.029	—	—	$2\tau^4(1 + mt^2)^3t^2$	0.022
Parameter estimates			r	<0.001		
			c	0.167	τ	0.506
			h	0.384	m	0.016
			h^2	0.147	t	0.409
			$h^2 + c^2$	0.175	t^2	0.168

*Path models described in Rao et al. (28). Parameters *k* and *z* set to one; *m* and *b* set to zero; $g = h\sqrt{(1 + m)/2} \approx 0.71 \cdot h$. *P* (proportion of opposite-sex twins) = .35.
†Path models described in Rice et al. (29).

Table 5. Recurrence Risks of Extreme Longevity (Excess Longevity > the 99th Percentile) in Various Classes of Relatives

Category	Degree	Controls	Cases	RR	95% CI	Model Prediction I	Model Prediction II
Sib/Parent	1	0.013	0.031	2.31	1.97–2.67	2.32	2.44
Uncle/Aunt	2	0.015	0.023	1.51	1.28–1.78	1.66	1.56
First cousin	3	0.012	0.018	1.51	1.34–1.71	1.33	1.25
–once removed	4	0.012	0.013	1.11	1.02–1.23	1.16	1.12
Second cousin	5	0.011	0.013	1.18	1.05–1.29	1.08	1.06
Log likelihood						–8.92	–10.94

Notes: All relatives of the specified type with follow-up data were selected for all individuals whose excess longevity exceeded the 99th percentile (17.5 years), and 5000 controls selected from the bottom 97% of the distribution of excess longevity. Model I is a single major gene model, and Model II is a model with an infinite number of alleles of small effect, as per Risch (1990). See text for additional description.

Model I (single locus) and Model II (infinite loci of small effect), along with the maximized log likelihood values for each model. The predicted relative risks for Model III (one major locus and infinite loci of small effect) are not shown because the maximum likelihood under Model III was achieved when the multiplicative effects were all set to one—equivalent to Model I. The difference in fit between Model III (equivalent in this case to Model I) and Model II is of marginal statistical significance: $\chi^2_1 = 4.04$, $p = .044$.

Table 6 and Figures 2A and 2B show our estimates of λ_s for sibling pairs reaching the various percentiles of excess longevity. The recurrence risk, λ_s, among sib pairs over age 65 of achieving the 97th percentile of excess longevity (+14.8 years) was 2.30 (95% CI 2.08–2.56). For a male born in 1900, who was affiliated with the LDS church, this level of excess longevity corresponds to age 95. For a female born in 1900, who was affiliated with the LDS church, this level of excess longevity corresponds to age 97. Figure 2A shows the estimated λ_s for pairs of sibs with differing values of excess longevity, such as would be encountered in conducting a sib pair study.

Table 6. Recurrence Risk Estimates for Excess Longevity in Siblings at Various Percentiles of the Distribution

Percentile	Excess Longevity	Number of Sib Pairs	Relative Risk (λ)	95% CI
A. Entire Cohort				
85%	9.0	13,190	1.29	1.24–1.34
90%	10.7	6,849	1.45	1.38–1.54
95%	13.2	2,134	1.66	1.55–1.80
97%	14.8	1,023	2.30	2.08–2.56
99%	17.5	135	2.36	1.89–2.95
B. Pairs of Sibs Whose Mendelian Excess Longevity (*ml*) Was Greater Than the 85th Percentile (2.3 years)				
85%	9.0	3,335	1.59	1.52–1.67
90%	10.7	1,905	1.86	1.74–1.98
95%	13.2	675	2.24	2.02–2.44
97%	14.8	378	3.36	2.96–3.79
99%	17.5	64	3.98	2.96–5.21

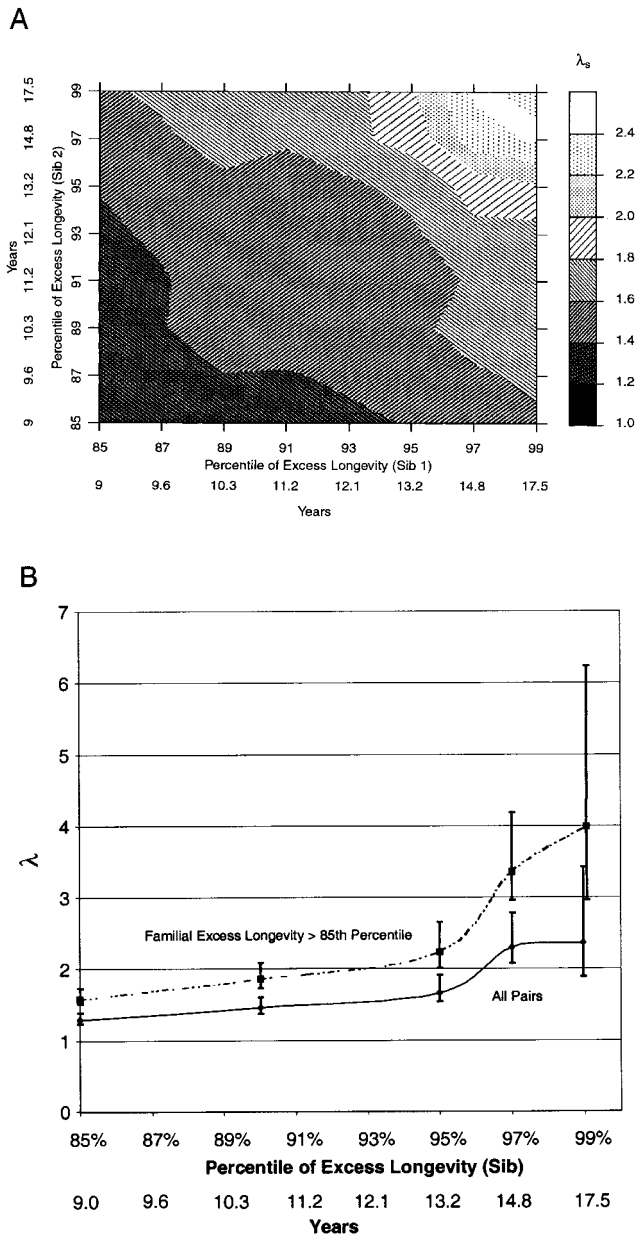

Figure 2. **A**. Filled contour plot showing λ_s for sib pairs with differing values for excess longevity. **B**. Estimates of λ_s and 95% confidence intervals at varying percentiles of excess longevity for random pairs of siblings, and for pairs of siblings whose familial excess longevity (excluding sibs) was greater than the 85th percentile (+2.3 years).

Table 6B gives the λ_s estimates for sibships selected because the kinship-weighted excess longevity among their family members (excluding sibs) was greater than the 85th percentile of familial excess longevity (2.3 years). The values of λ_s observed in these selected sib pairs are higher than those reported in Table 6A by a factor ranging from about 1.2 at the 85th percentile of proband longevity to about 1.7 at the 99th percentile. In Figure 2B the values of λ_s are shown, along with CIs for both the sib pairs selected from the entire cohort and the sib pairs with high familial excess longevity.

Except for the 99th percentile of proband longevity, the CIs for the λ_s estimates in the two sets of sibs do not overlap.

Discussion

We have shown that excess longevity aggregates in families, and that the pattern of this familial aggregation is consistent with a relatively simple model of inheritance involving the additive effects of one or more loci. Overall, a modest portion (10–20%) of the variability in excess longevity appears to be heritable. Of particular interest is the portion of the variability in excess longevity that may arise from inter-individual differences in rates of aging. By including for analysis only individuals who survived to at least age 65, we have attempted to reduce the proportion of the variability in excess longevity that is unrelated to variation in the rate of aging. Nevertheless, at least a portion of the remaining variability in excess longevity among those over age 65 will be due to variation in susceptibility to common life-threatening diseases, unrelated to rates of aging. Therefore, the results presented here do not allow us to distinguish long-lived sibships without genes for slower aging from long-lived sibships with genes for slower aging; ways of addressing this problem are considered below.

The exclusion of individuals under the age of 65 has the potential to bias our results, if the characteristics of those included differ in important ways from those of the source population. The primary difference that we observed between the source population and the data we analyzed was the greater likelihood that an individual affiliated with the LDS church would survive to age 65, compared to non-LDS individuals. LDS affiliation continues to influence longevity after the age of 65, and our estimates of excess longevity are adjusted for this effect. Both our cohort and our reference population contain large numbers of people not classified as LDS-affiliated by our criteria. Nevertheless, it is possible that the differential loss of non-LDS individuals from our data set, which may be due in large part to behavioral differences such as tobacco and alcohol use, has led us to underestimate the magnitude of the influence of behavioral variability on longevity in the Utah population in general. If this is so, then our estimates of the heritability of longevity should be higher than those observed in other studies of samples with similar characteristics, such as Bocquet-Appel's (20). Because our estimates of the heritability of longevity are somewhat lower than the majority of published estimates, it seems unlikely that a bias of this sort has had an important influence on our results.

The inclusion of living subjects among our cohort, motivated by considerations of power and the possible use of living subjects for linkage studies, has the potential to introduce a bias away from the null. A sibling of a subject born after 1900 has a greater probability of being censored (hence having an artificially small value of excess longevity) than a sibling of someone born earlier. Because the same is true for the subjects themselves, this could introduce spurious correlations of excess longevities among sibs. Alternatively, a conservative bias could be introduced because our measurement of longevity is less precise (due to censored observations) in families with a high proportion of longevity. We evaluated the potential for bias by excluding sibs born after 1900 from the regression analyses and found no meaningful differences among the effect estimates (results not shown).

We have attempted to reduce confounding from nongenetic familial influences on longevity by adjusting for affiliation with the LDS church (which discourages the consumption of alcohol and tobacco by its members), and for average excess longevity among the spouses of a subject's relatives (as a proxy for environmental influences that aggregate in families); however, these adjustments do not remove all possible confounding by environmental factors. It is also possible that members of the LDS church are genetically more similar to one another than to nonmembers, in which case we may have overcorrected our excess longevity estimates, leading to underestimation of heritability and recurrence risks.

Furthermore, although path analysis does not meaningfully alter our h^2 estimates of excess longevity, we have observed that the fit of expected to observed correlations between the sexes and across generations is probably affected by residual gender and birth year effects not completely eliminated by the use of excess longevity. Examining the heritability of familial frailties (10) may ultimately prove to be more productive than examining the heritability of longevity per se.

We have found that the observed patterns of recurrence of extreme longevity in various classes of relatives are consistent with a single-locus model of inheritance. As we have noted, however, these results do not indicate that variability in excess longevity is the result of variation at only a single locus—rather, they suggest that inheritance of a single variant allele at one of an unknown number of loci is sufficient to affect the probability of living to an extreme age. Although the particular loci at work may differ between families, this result is encouraging for those who wish to pursue linkage or association studies in order to identify loci responsible for excess longevity. It is also worth noting that the fit of a model of infinite loci with tiny multiplicative effects, representing a "worst-case" scenario for linkage and association studies, is not much worse than that of the single-locus model.

The maximum λ_s we observed among random pairs of sibs is about 2.3 (the 95% CI for the 97th percentile is 2.1–2.7). This is considerably lower than was found by Perls and colleagues (32) for sibs reaching similar age thresholds. In that study of sibs of centenarians from Massachusetts, λ_s ranged from 3.5 for survival to 84, to 4.0 for survival to age 94. There are differences in design and data between these two studies that may account for much of the difference in the magnitude of the observed recurrence risks. The Perls study used as a reference group the siblings of individuals who died at exactly age 73, whereas we have based our comparisons on sib pairs drawn from the entire contemporaneous population. The restricted variability in Perls' reference set increases the chance that unobserved confounding factors or random fluctuation widened the gap between the sibships of centenarians and the reference sibships used in that study. Moreover, the magnitude of the effects of unobserved confounding factors such as tobacco and alcohol consumption might be greater in the Massachusetts-based sample employed by Perls than in our Utah-based population. Perls also reported a substantial difference between average sibship sizes for centenarians (4.5 siblings per proband) and

controls (3.2 siblings). We found no difference between the average sibship size for subjects with excess longevity greater than 14.8 years (8.05 siblings per proband) and subjects with excess longevity between –1.0 and +1.0 years (8.00 siblings).

If familial excess longevity information is used to select sibships for study, the probability of recurrence of longevity among sibs of a long-lived proband increases. There are several important implications of this observation. First, the enhancement of recurrence risks by incorporating information on the longevity of more distant relatives suggests that the trait is transmissible through multiple generations (relative recurrence risks significantly greater than unity in distant relatives confirm this). Second, the use of familial excess longevity information to stratify a set of sib-pairs (assuming a sufficient number of pairs are available) might enhance the probability of finding linkage by increasing the probability that the sib pairs used really are segregating predisposing alleles.

Given favorable assumptions about heterogeneity, our results suggest that adequate power for a successful nonparametric linkage analysis of excess longevity might be achieved with a moderate number of sib pairs, using anonymous polymorphic markers throughout the genome and/or markers for specific candidate loci. Similar approaches have already mapped naturally occuring genetic variants contributing to longevity in fruit flies and mice (33–36). It should also be possible to identify large pedigrees with multiple members who have excess longevity greater than some critical value. If, as seems likely, relatively rare alleles at multiple loci enhance longevity, parametric or nonparametric linkage in such large kindreds may prove to be more useful in mapping genes for longevity than sib-pair methods.

An alternative to linkage analysis is to perform genetic association studies to test whether a specific allele or class of alleles at a strong candidate locus is more frequent in long-lived cases from sibships at high risk for genetically transmitted excess longevity, as compared to the allele frequency in controls. For example, the $\epsilon 2$ allele at the apolipoprotein E locus is increased in frequency in centenarians (37) and associated with lower mortality from multiple causes in longitudinal studies of elders (38,39). Similar work should be done to test whether human genetic loci homologous to loci associated with extended life span in other species (for review, see ref. 40) also harbor alleles significantly associated with longevity. The use of information on both individual and familial longevity to select individuals for association studies has the potential to increase the power of such studies as well.

Because of the complexity that underlies life span as a phenotype, the success of genetic linkage and association studies of longevity may be enhanced by restricting analyses to families that show signs of slower aging beyond simple longevity. Such families could include, for example, those in which quantitative biomarkers associated with age-specific mortality from multiple causes fall within ranges that predict better than average survival. Appropriate traits include high age at last natural pregnancy taken to term (41), high age at natural menopause (42,43), low resting body temperature (44), low resting heart rate (45–48), low peripheral blood leukocyte count (49–52), and high percent-predicted forced expiratory volume in one second (FEV1; 51,53–55). Several of these biomarkers have also been shown in twin studies to be largely under genetic control [menopause (56,57); heart rate (58); leukocyte count (59); and FEV1 (60)]. Another feature predicted for families carrying genes that slow aging is lower age-specific mortality from multiple age-related diseases (heart disease, cancer, stroke, etc.), as compared to control families. Relatively long-lived families with biomarker values predicting better survival, and lower age-specific mortality from multiple causes, should be most likely to harbor genes that slow aging.

Conclusions

We have shown that excess longevity among a large cohort of individuals drawn from the UPDB has a substantial familial component. The patterns of inheritance are consistent with Mendelian inheritance of genes affecting longevity. We have adjusted our estimates for both direct and indirect environmental influences on longevity, although residual effects of shared environment may still be present in our data. Our results lend support to the notion that genes contributing to extreme longevity in humans may be identifiable by genetic linkage and genetic association approaches.

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