

Heritability of Life Span in the Old Order Amish

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Although a familial contribution to human longevity is recognized, the nature of this contribution is largely unknown. We have examined the familial contribution to life span in the Old Order Amish (OOA) population of Lancaster County, Pennsylvania. Analyses were conducted on 1,655 individuals, representing all those born prior to 1890 and appearing in the most widely available genealogy, surviving until at least age 30 years, and with known date of death. Mean age at death (\pm SD) in this population was 70.7 ± 15.6 years, and this did not change appreciably over time. Parental and offspring ages at death were significantly correlated, as were ages of death among siblings. Offspring longevity was correlated with longevity of both parents, and in more or less additive fashion. For example, mean offspring age at death was 69.4 ± 15.3 years in individuals for whom both parents died before the age of 75 years ($n = 280$) and increased to 73.5 ± 16.0 years in individuals for whom neither parent died before the age of 75 years ($n = 311$). These differences were highly significant ($P = 0.006$). We estimated heritability of life span to be $25\% \pm 5\%$, suggesting that the additive effects of genes account for one quarter of the total variability in life span in the OOA. We conclude that longevity is moderately heritable in the

OOA, that the genetic effects are additive, and that genetic influences on longevity are likely to be expressed across a broad range of ages. Published 2001 Wiley-Liss, Inc.[†]

KEY WORDS: Amish; longevity; heritability

INTRODUCTION

There is considerable variation in human life span, and identification of the factors involved may ultimately suggest ways to slow the physical and mental decline that occurs in later years. Genetic factors almost certainly contribute to this variability, although the nature of the genetic influences on longevity is largely unknown. Such genes could be related directly or indirectly to disease susceptibility or progression, or more generally to cellular maintenance and repair.

Family-based studies have, in general, provided support for a modest genetic influence on life span. Longer-lived parents tend to have longer-lived offspring, although the magnitude of these correlations tends to be small [Pearl, 1931; Abbott et al., 1974; Philippe, 1978; Mayer, 1991; Gavrilova et al., 1998]. Moreover, the pattern of the familial correlations has not always been consistent, with one study reporting far stronger correlations between mothers and sons than among other types of relative pairs [Abbott et al., 1974], and a second reporting the mother-daughter correlations to be markedly stronger [Crawford and Rogers, 1982]. However, in at least one family study, the heritability of life span was estimated to be close to zero [Philippe, 1978].

Familial influences on life span have also been estimated from twin studies. Such studies have indicated that life span tends to be more correlated in monozygotic than dizygotic twin pairs, with these differences yielding heritability estimates ranging from 25%–60% [McGue et al., 1993; Herskind et al., 1996; Ljungquist et al., 1998; Iachine et al., 1998]. Notably, in

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TABLE I. Previous Studies of Heritability of Human Longevity

Author	h^2	Sample	Comment
Abbott et al. [1974]	10%	1,766 old aged subjects and their 7,103 offspring born 1822–1915	
Philippe [1978]	≈ 0	French Canadian isolate; offspring of parents who married 1820–1869	
Mayer [1991]	16–32%	Genealogies of 6 large New England families born 1650–1874	No secular trends; value of h^2 depends on which classes of relative pairs used in the calculation
Herskind et al. [1996]	26% men; 23% women	2,872 same sex twin pairs (Denmark) born 1870–1900	Minimal censoring
McGue et al. [1993]	33%	600 same sex twin pairs (Denmark) born 1870–1880	
Iachine et al. [1998]	$\approx 50\%$	31,608 same sex twin pairs (Denmark, Sweden, Finland)	
Ljungquist et al. [1998]	10–35%	10,505 same sex with twin pairs born 1886–1925 (Sweden)	$h^2 = 35\%$ when calculated from all twin pairs, but $h^2 = 0\%$ (men) and 15% (women) when calculated from twin pairs reared apart

at least one of these twin studies, the correlations between monozygotic twins were consistently more than double those observed in dizygotic twin pairs [Herskind et al., 1996]. This observation could reflect the influence of non-additive genetic effects, such as those due to dominance or to epistasis, or alternatively, it could reflect a larger impact of environmental (non-genetic) influences on life span in monozygotic than dizygotic twin pairs. In fact, this latter explanation is supported by the results of at least one study, in which heritability was estimated to be about 35% among the total sample of 10,505 twin pairs, but only 0%–15% when the analysis was restricted to the subset of twin pairs who were reared apart [Ljungquist et al., 1998]. A further limitation of some of these studies is the inclusion of significant numbers of living individuals, leading to a reduction in the overall variability in life span, and thus potentially affecting the heritability estimate. Table I summarizes briefly the findings and salient features of prior family and twin studies that have provided estimates of heritability of human longevity.

It is not clear at present if the relative impact of genetic influences on life span is constant throughout adulthood. There is clearly a genetic influence on premature death, as demonstrated by Sorensen et al. [1988], who observed that death prior to the age of 50 was associated with a 1.7-fold increase in the risk of all-cause premature death for biological children, but there was no corresponding increase in risk of premature death for adopted children. Similarly, it has been observed that relatives of centenarians tend to live longer than relatives of controls [Perls et al., 1998; Robine and Allard, 1998], and, in fact, a few studies have reported that variants in a few specific genes (e.g., apoE and ACE) may be over-represented among the very old [Schachter et al., 1994; Gerdes et al., 2000]. Whether genetic effects on human life span reflect the actions of genes that are expressed across the life span or only at certain periods of life is unclear.

The Old Order Amish (OOA) of Lancaster County, Pennsylvania, represents an ideal population for

investigating genetic effects on longevity. The OOA originated in 1693 in Western Europe (mainly Switzerland) as an offshoot of the Mennonite movement. Between 1727 and 1777, approximately 200 Amish families immigrated to the United States and settled in Lancaster County, where 30,000 of the present day descendants of these founder families reside [Cross, 1976]. Other large groups of immigrant Amish settled or eventually migrated to Western Pennsylvania, Ohio, Indiana, and Maryland. The population is relatively closed, with very few marriages occurring between Amish and non-Amish. Extensive genealogical records are maintained by the OOA community, including the birth and death dates of nearly all descendants of the Lancaster County OOA [Beiler, 1988; Beiler, 1996; Agarwala et al., 1999]. We have made use of this extensive genealogical information to examine the familial determinants of longevity in this unique population. Initially, we estimated the parent-offspring correlations in life span, and the overall heritability of life span in the OOA. Secondly, we estimated age of offspring death as a function of parental age at death, to determine whether the genetic influences on life span are limited primarily to deaths occurring at young ages or to deaths occurring at old ages.

METHODS

Genealogical information about the OOA in Lancaster County was obtained from one version of the Fisher family history [King et al., 1996], supplemented by extensive fieldwork (by T.M.K.) to fill in and correct missing birth and death dates. Our working database included 52,450 individuals born prior to February 29, 1988. Vital status was updated through Dec. 31, 1988, at which time a total of 6,015 deaths were recorded [King et al., 1996].

We restricted our analysis to individuals born prior to 1890 to minimize the potential for including in the analysis persons who were still living. Of the 2,543 individuals born prior to 1890, we excluded 406 (16%) for whom date of death was unavailable. Also excluded

from our analysis were an additional 482 individuals known to have died prior to their 30th birthday, many of whom had died in infancy. Thus, the analyses presented in this report are based on 1,655 individuals, representing all OOA in this genealogy born prior to 1890, with known date of death, and surviving until at least the age of 30 years.

Cohort and sex effects on life span were evaluated by analysis of variance. We next divided the dataset into nuclear families ($n=383$) and computed the familial correlations in age at death among family members using the FCOR program of S.A.G.E. [1998]. Correlations were computed for spouse, parent-offspring, and sibling pairs, with equal weighting given to each family (i.e., the components making up the correlations were averaged within families before being averaged across families).

Nearly all of the 1,655 individuals with known age at death could be connected into a single 7-generation pedigree. Using this pedigree, we then estimated the heritability of life span using a pedigree-based maximum likelihood procedure [Lange et al., 1976; Hopper and Mathews, 1982]. Heritability (h^2) was defined as the proportion of the total trait variance (σ^2_T) attributable to the additive effects of genes (σ^2_G) (i.e., "narrow sense" heritability; $h^2 = \sigma^2_G / \sigma^2_T$). We modeled the observed phenotypic covariances between two individuals within the pedigree as having an expected value given by the product of their coefficient of relationship (which is equal to two times their kinship coefficient), the heritability, and the phenotypic variance of the trait (conditional upon covariate effects). Based on this simple model, the likelihood of the pedigree data was computed under the assumption of multivariate normality. Parameter estimation was performed by finding those values of the parameters (including the heritability) that yielded the maximum likelihood. These analyses were conducted using the SOLAR software program [Almasy and Blangero, 1998]. This pedigree-based method for computing heritability is more efficient than classical quantitative genetic methods that are based on only a single class of relatives, since all pedigree information is considered jointly. In contrast, heritability is estimated in twin studies as a function of the differences in trait correlations among monozygotic and dizygotic twin pairs. Estimates obtained from such studies are sensitive to the critical assumption that the impact of environmental influences on variation within twin pairs is identical for monozygotic and dizygotic pairs, since one would like to infer that phenotypic differences between monozygotic twins (who share all their genes in common) are attributable only to differences in environmental exposures, while differences between dizygotic twins (who share only one-half of their genes in common) may be attributable to differences in both genes and environment.

We compared mean age of death in the offspring according to age of death of both parents. Initially, we calculated the mean age of death among offspring depending on the number of their parents (0, 1, or 2) who had died prior to a particular age (from 45–90

years, in 5-year increments). Then, to evaluate more fully the independent contributions of age at death of each parent, we cross-classified offspring into mutually exclusive categories depending on the decade of age at death of each parent.

RESULTS

The distribution of age at death in these OOA subjects is shown in Figure 1. The mean (\pm SD) age at death in this cohort was 70.7 ± 15.6 years. There were no significant effects of either sex ($P=0.32$) or year of birth ($P=0.98$) on age at death (Table II). Figure 2 shows the probability of surviving as a function of age for the 1,655 pedigree members included in these analyses. Women had slightly higher mortality rates than men until approximately age 62 years, at which point the sex differential virtually disappeared.

Correlations in age at death among family members are shown in Table III. Correlations among spouse pairs were essentially zero ($r=0.010$), but were substantially higher among parent-offspring ($r=0.096$) and sibling ($r=0.087$) pairs. There was little evidence for a parent of origin effect, although correlations were somewhat lower for father-son pairs ($r=0.049$) than for any of the other types of parent-offspring pairs ($0.099 \leq r \leq 0.123$). Among siblings, correlations in age at death were highest for brother-brother pairs ($r=0.142$), and lowest for sister-sister pairs (0.056). When pairs were weighted equally, instead of by nuclear family, correlations were virtually identical between parent-offspring ($r=0.096$) and sibling-sibling ($r=0.087$) pairs.

Based on the full pedigree data, the maximum likelihood estimate of the heritability of life span was 0.25 ± 0.05 , suggesting that the additive effects of genes accounted for 25% of the total variation in age at death.

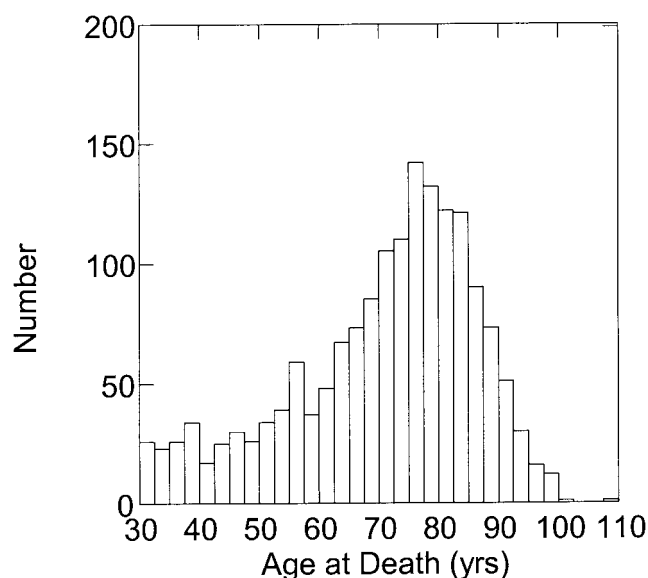


Fig. 1. Distribution of age at death in 1,655 OOA individuals, born between 1749 and 1890.

TABLE II. Mean Age at Death (\pm SD) for Individuals Surviving to at Least 30 Years of Age and Born Between 1745 and 1890*

Year of birth	Men	Women
1745–1799	69.4 \pm 19.2 (18)	72.6 \pm 13.0 (15)
1800–1819	73.1 \pm 11.6 (41)	71.7 \pm 15.9 (45)
1820–1839	70.9 \pm 13.6 (108)	71.4 \pm 15.5 (95)
1840–1859	68.8 \pm 13.4 (186)	69.2 \pm 17.4 (191)
1860–1879	71.6 \pm 14.1 (291)	69.8 \pm 16.5 (296)
1880–1889	72.4 \pm 15.9 (189)	71.2 \pm 17.7 (180)
Total	71.1 \pm 14.4 (833)	70.3 \pm 16.8 (822)

*Number of deaths in parentheses.

Heritability differed little by sex when computed for men and women separately.

Parental age at death was significantly associated with offspring age at death throughout the life span. For parents experiencing an early death (age 45 years or younger), the mean age at death in their offspring was 69.5 \pm 16.7 years (n = 141 offspring). At the other extreme, if a parent survived until age 95 years or older, the mean age of offspring death was 78.9 \pm 15.7 years (n = 23 offspring). Furthermore, there appears to be a clear contribution of both parents. Figure 3 shows the mean age of death of offspring according to whether neither, one, or both of their parents had died at a given age. At each of 10 different ages (age 45–90 years, in 5-year increments), we classified the 1,164 subjects for whom age at death was known in both parents according to the number of their parents who had survived until that age. Offspring longevity was strongly related to the age of death of both parents. At any given age, the offspring age at death was consistently lower (generally by 1–2 years) if one parent had died prior to that age than if neither parent had, and lower still (generally, by another 1–2 years) if both parents had died prior to that age. For example, the mean offspring age at death was 73.5 years if neither parent had died by age 75. Death of one parent before the age of 75 was associated with approximately a two-year-younger age at death for the offspring (71.5 years), and the death of both parents prior to the age of 75 was associated with an additional two-year-younger age at death (69.4 years).

Figure 3 also illustrates that the impact of a parental death was particularly strong when it occurred at a relatively young age. For example, the mean age of death (\pm standard error) in offspring was 61.3 \pm 6.1 years if both parents had died prior to age 50, 69.4 \pm 1.2 years if one parent had died prior to age 50, and 72.0 \pm 0.5 years if neither parent had died prior to age 50. No data are presented for the category “Both parents died by age 45” because this category included only one individual (whose age at death was 64.3 years). There were no offspring in this sample for whom both parents survived until at least age 90.

Reduced longevity in the offspring of parents dying at younger ages could be due predominantly to an increased risk of early death only in these offspring, or alternatively, it could reflect an overall reduction in life span that persists even if the offspring survives past the middle-age years (and hence is no longer “at risk”

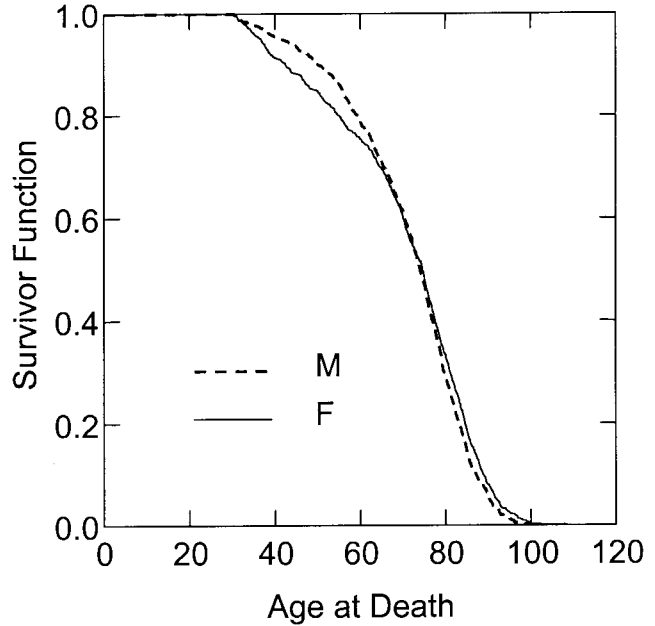


Fig. 2. Survival probabilities for 1,655 Amish men and women born between 1749 and 1889.

for an early death). To explore this issue, we cross-classified each of the 1,164 individuals based on the decade of death of each parent. Results of this analysis are shown in Table IV, which summarizes mean age according to age of death of both parents. Although there are several exceptions, these results suggest that the increased mortality risk associated with an early parental age at death appears to extend even into later ages. In other words, early mortality in a parent is associated with reduced life span in the offspring, even if the offspring survives past middle age.

DISCUSSION

The present study is one of a small number of studies in which heritability of life span has been estimated using large extended families rather than collections of twins. Genetic effects can sometimes be overestimated from twin studies if monozygotic twins share a larger environmental resemblance in trait risk factors than do dizygotic twin pairs. The heritability of life span from our study was 25%, a value nearly identical to that obtained from a study of Danish twin pairs reported by Herskind and colleagues [1996], but considerably lower than the 50% reported recently from an analysis of more than 31,000 twin pairs collected from Denmark, Sweden, and Finland [Iachine et al., 1998]. An important strength of our study is that it is one of the few with relatively little censoring; that is, the study period was limited such that no subjects were currently alive at the end of the follow-up period. The selection of nuclear families using the Fisher family history implies that all persons studied are descendants or spouses of descendants of Christian Fisher. One cannot exclude the possibility that Christian Fisher or his spouses

TABLE III. Correlation in Age at Death Among Spouses, Parents and Offspring, and Siblings

Relative pair	Number of pairs	Correlation
Mother-father	312	0.010
Parents-offspring	2,435	0.096
Mother-daughter	586	0.123
Mother-son	614	0.099
Father-daughter	610	0.106
Father-son	709	0.049
Sibling-sibling	2,825	0.087
Sister-sister	709	0.056
Sister-brother	1,416	0.082
Brother-brother	700	0.142

carried alleles/genes very relevant to longevity that would make the longevity of his descendants more heritable than for the other Old Order Amish or for non-Amish persons.

No sex or cohort effects on life span were observed in these data. Similarly, birth year was not associated with age at death among Danish twins born 1870-1900 [Herskind et al., 1996] nor among family members born prior to 1874 in the family study reported by Mayer [1991]. There was no appreciable sex difference in life span, unlike in many other populations in which females tend to live longer than males. Mortality rates were slightly higher in younger Amish women compared to their male counterparts, a differential that

might be partially explained by increased mortality associated with the child-bearing years.

A striking result from our analysis was that the parent-offspring correlations in age at death were very similar to those observed for sibling pairs. In fact, when equal weighting was applied to pairs, the correlations were virtually identical between the two types of relative pairs. Interestingly, parent-offspring and sibling correlations were also observed to be similar in an analysis of French Canadian families reported by Philippe [1978], but these correlations were also similar in magnitude to those observed between spouse pairs, suggesting that life span in these families had a heritability close to zero. In further contrast to our results in the OOA are reports from other studies suggesting unusual patterns in the correlations in age at death for different classes of relatives. For example, Herskind et al. [1996] observed that correlations in life spans among monozygotic twins were greater than two times the correlations observed in dizygotic twins, suggesting either the presence of non-additive genetic effects, or alternatively, a more similar environmental influence on monozygotic than dizygotic twin pairs. In a second study, Mayer [1991] observed higher correlations among siblings than among parents and offspring, resulting in heritability estimates of 16%-22% for life span in families from New England when calculated on the basis of parent-offspring regressions, but 33%-41% when estimated from sibling intraclass correlations. Larger correlations among siblings than between

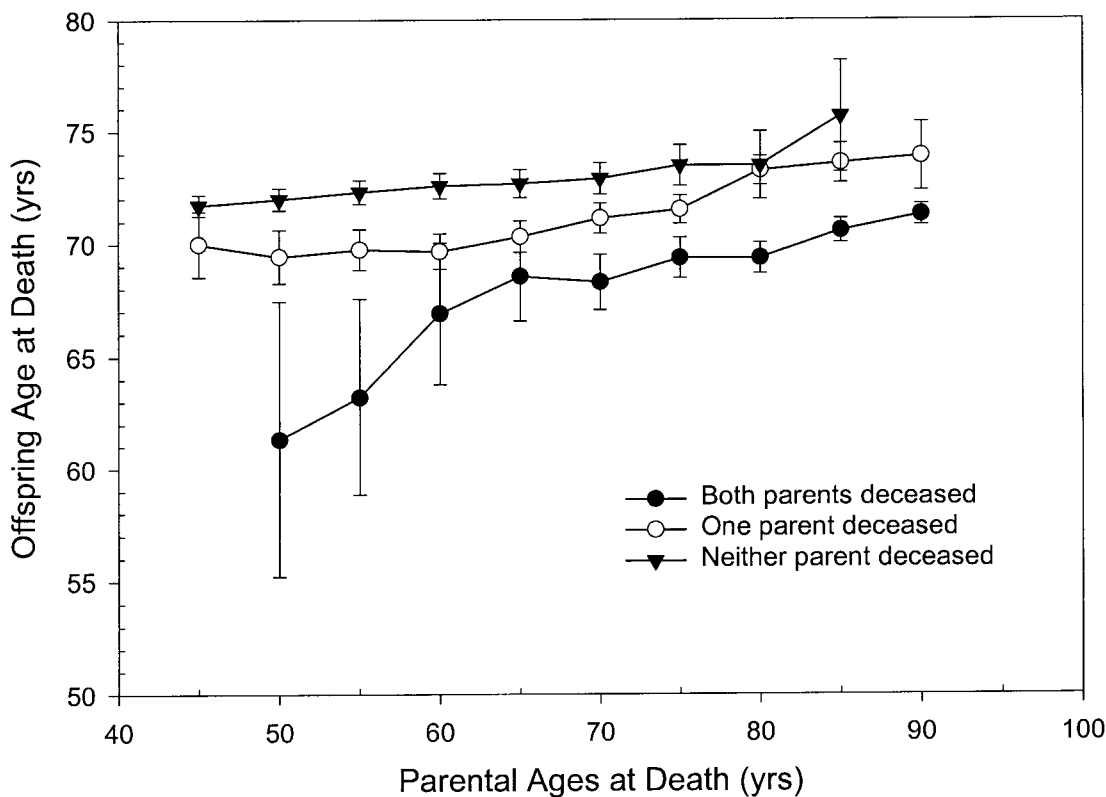


Fig. 3. Mean age at death according to parental age at death.

TABLE IV. Mean Offspring Age at Death According to Decade of Parental Death*

Age at death— parent 2	Age of death—parent 1					
	40–49	50–59	60–69	70–79	80–89	90–103
40–49	61.3 (10)	71.8 (16)	65.5 (18)	68.7 (94)	71.5 (44)	76.7 (2)
50–59		61.4 (4)	68.6 (58)	66.5 (43)	72.2 (103)	72.9 (4)
60–69			69.6 (56)	73.9 (79)	71.2 (76)	72.7 (41)
70–79				69.4 (148)	74.1 (225)	78.8 (31)
80–89					74.6 (86)	69.9 (26)

*Number of individuals in parentheses.

parents and offspring can also suggest the presence of important non-additive genetic effects, such as effects due to epistasis and/or dominance, because parent-offspring correlations capture additive effects only (since only a single allele is transmitted), while siblings have the opportunity to share two alleles in common at any given locus, thus allowing the possibility for transmitted alleles at the same locus to interact with each other (dominance) or with alleles at other loci (epistasis). However, an alternative explanation for higher sibling than parent-offspring correlations would be the presence of secular trends in environmental influences that could provide an additional source of variation in trait values between parents and offspring but that would have less impact on variation within sibling pairs. In the OOA, the environment may not have changed as much between generations as it has for more technology-oriented populations, resulting in parent-offspring and sib-sib correlations being more similar.

The relative importance of genetic influences on life span may vary at different ages. Premature death in a parent is a strong risk factor for early death in the offspring, and possibly, because sporadic causes of death in middle age are relatively infrequent, the genetic contribution may account for a relatively larger share of the mortality occurring at these ages than at older ages. In a large twin sample consisting of male U.S. military veterans who had died between the ages of 20 and 60 years, the heritability of liability of death was estimated to be 50% [Hrubec and Neel, 1981]. In the OOA, we observed a relatively large effect of early parental age at death on offspring longevity. The mean age of death in subjects for whom both parents had died before the age of 50 was 61 years, approximately eight years younger than in subjects for whom only one parent had died before age 50, and more than 10 years younger than in subjects for whom both parents had survived past age 50 years.

Although the relative importance of genes on overall mortality may vary at different ages (i.e., may account for proportionately more of the variability in life span in subjects dying at early versus later ages), it is possible that many of the genes involved may alter risk of death at different ages, rather than by determining age at death directly. For example, genes affecting mortality risk at younger ages may also confer risks that extend into later years. In the study of McGue and colleagues, the death of a monozygotic twin in middle age (i.e., aged 40–60 years) was associated with a significant risk of

premature mortality in the co-twin. But even if the co-twin survived past age 60, 70, or even 80 years, the risk of mortality remained elevated [McGue et al., 1993]. It is also likely that there are different gene variants that exert their effects at different ages. For example, at younger ages, variants in genes related to disease susceptibility may be the primary genetic determinants of mortality risk. In the very old, however, gene variants related to cellular damage and repair functions may be the more important genetic determinants. In support of this latter hypothesis, studies of centenarians indicate that the very old are often healthier and more active than individuals 10–20 years younger, and furthermore, that mortality rates among the oldest old are much lower than would be expected by extrapolating from the death rates of younger individuals [Perls, 1995; Perls et al., 2000]. These observations suggest that mortality determinants in the very old may be very different from those playing a major role in younger individuals. A general limitation of the human longevity studies is the non-availability of information regarding cause of death. If such information were available, it might allow more thorough analysis of the genotype-phenotype relationship in human longevity.

Efforts to identify variants in specific genes that influence variation in life span in humans are in their early stages. The traditional approach of linkage mapping is impractical because of the difficulty in obtaining appropriate family collections with both phenotypes (e.g., age at death) and genotypes. Instead, much interest has centered on development of animal models of aging, particularly utilizing yeast, nematodes, fruitflies, and mice. In each of these models, specific genes have been identified that modulate life span. One of the most remarkable life span extensions has been achieved by altering genes in the *daf-2* gene network that modulate the primitive insulin signaling pathway in the nematode, *C. Elegans* [Honda and Honda, 1999]. Mutations in several genes, including *daf-2* and *daf-16*, have been identified that increase life span by more than two-fold in this species by regulating oxidative stress resistance [Lin et al., 1997]. Mutations in genes encoding other signaling transduction proteins have also been identified in *Drosophila* flies [Clancy et al., 2001; Tatar et al., 2001] and yeast [Jazwinski et al., 1993]. It is possible that mutations in individual genes in the oxidative stress pathway may also prove to be significant (or at least measurable) contributors to variation in human life span, although results obtained

from lower order organisms must be cautiously applied to humans because of the more complex systems in humans, the larger number of genes involved, and the fact that life span and causes of death in humans are different from those in lower species. However elusive, the identification of specific genes that influence longevity remains a worthy pursuit as such genes could conceivably provide important insights that might be used for prolonging quality of life in elderly individuals.

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