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Genetic Influences on Life Span and Survival Among Elderly African-Americans, Caribbean Hispanics, and Caucasians

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An investigation of the genetic influences on life span and survival was conducted among elderly African-Americans, Caribbean Hispanics, and Caucasians Medicare recipients (ages 65–104 years). Family history information on 13,161 parents and siblings was obtained. Heritability of life span varied by the age and by ethnic group being lowest for African-Americans. We recalculated the heritability coefficients for life span including only probands and their siblings, but the differences across ethnic groups persisted. In contrast the heritability of survival was more similar across ethnic groups but was similar to that for life span. Heritability coefficients for survival in probands and their siblings revealed little difference between ethnic groups and suggested that as much as 35% of the variation in survival may be genetically influenced. These results indicate that life span and survival are genetically influenced. Comparisons across generations and ethnic groups indicate that changes in environmental hygiene, social welfare, and health care systems are significant contributors to life span and survival, but genetic influences are also important. Identifying the genes associated with life span and survival will provide insight into how the genes interact with environment to influence aging in humans.

KEY WORDS: genetic influence; heritability; aging; ethnic groups

INTRODUCTION

Over the last 50 years, developed countries have seen a trend toward increasing survival into old age due to the dramatic decrease in mortality rates among the older individuals [Vaupel et al., 1998]. Studies of life span in model organisms and, to a lesser extent, in humans suggest that genetic variation is also likely to be important [Finch and Ruvkun, 2001]. Variations in genes involved in metabolism or in insulin-signaling pathways in nematodes (*Caenorhabditis elegans*) [Kimura et al., 1997] and in fruit flies (*Drosophila*) [Tatar et al., 2001] can extend life span. In humans, Perls et al. [1998] observed that siblings of centenarians were four times as likely to live past 85 years than siblings of individuals who died at younger ages. The degree of genetic influence or heritability of life span has been estimated in human investigations of twins and isolated or founder populations [De Benedictis et al., 2001]. The correlation of total years of life span was twice as high in monozygotic twins compared with that in dizygotic twins [Herskind et al., 1996], and the concordance does not diminish with advancing age [Herskind et al., 1996; Ljungquist et al., 1998]. These investigations suggest that a third of the variance in life span can be attributed to genetic factors.

Heritability provides an estimate of the degree to which the variability in a phenotype in a population is related to genetic variation. It is difficult to fully separate shared genetic from shared environmental influences. Further, because the estimation of heritability depends on all contributing genetic and environmental components, a change in any one factor can influence the estimate [Falconer, 1989]. The life span of ethnic minorities in the United States has not been investigated previously. In the current study, we estimated the degree of genetic influence on life span, and then used a modified survival trait analysis combining the known life span of deceased relatives with current age of living.

MATERIALS AND METHODS

Study Population

Data were derived from participants in the Washington Heights-Inwood Columbia Aging Project. The names and addresses of all Medicare and Medicaid beneficiaries aged 65 years and older with mail addresses in the study area (Manhattan island north of 145th Street) were obtained from the Health Care Financing Administration. Six strata were formed on the basis of age (65–74 years and 75 years and older) and ethnic group (Hispanic, non-Hispanic Blacks, and non-Hispanic Caucasians). Systematic random sub-samples of roughly equal size were drawn for each of the six strata.

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The ethnic group of the participants was confirmed by self-report at the time of the initial interview. Using the 2000 United States Census questionnaire as a guide, individuals were asked if they consider themselves White (Caucasian), Black (African-American and non-Hispanic), or other and then asked if they were Hispanic. If Hispanic, the country in which they were born was queried. The majority of those (84%) who considered themselves Hispanic were from the Dominican Republic or one of the other Caribbean Islands.

Probands underwent an in-person, structured interview of health and function at the time of entry into the study. This was followed by a standardized medical history, physical and neurological examination, and neuropsychological battery that included tests of memory, language, reasoning and a screen for depressive symptoms. This evaluation has been previously described in detail [Pittman et al., 1992].

Probands also completed a detailed family history interview for each first-degree relative that included the current age or age at death, if deceased, and specific questions regarding several major illnesses such as Alzheimer's disease, Parkinson's disease, heart disease, hypertension, stroke, and cancer. If a relative was reported to be dead, the cause of death was ascertained if known. If the participant was uncertain of the information, other family members were queried. When relatives were reported to be over 100 years of age, the participants and other family members were contacted to re-confirm the ages of these individuals.

The validity of the family history was determined by direct examination of 99 relatives of 75 probands [Devi et al., 1998]. Current age of each relative ascertained from the family history was compared to that obtained during the interview and examination of that specific relative. The correlation coefficient for age reported by the proband compared to relative's actual age was 0.988, indicating very high agreement.

The study sample consisted of 2,753 individuals. The family history was not obtained from 391 (14.2%). Of these 342 (12.4%) individuals refused to provide information about their family members. Another 42 (1.5%) could not be located after the baseline visit for the family history interview, and seven (0.3%) individuals died before the interview could be conducted. These 391 individuals were slightly older (78.0 vs. 76.3 years) than the study sample, but the educational level, the proportion of women participants, and the distribution by ethnic group were similar to those of probands with a family history interview. The Columbia University Institutional Review Board reviewed and approved this project. All individuals provided written informed consent.

Statistical Analysis

We conducted heritability analysis for life span and survival. Life span was defined as the total number of years from birth to death. In contrast, survival was defined as the total number of years from birth to death for deceased individuals, and as the current age for living individuals. For heritability of life span, we restricted the analysis to families where all family members (parents and siblings) were deceased except for probands. For heritability of survival, we included both deceased and living family members and applied a survival analysis method similar to that described by Duggirala et al. [1999]. For deceased family members, age at death was used so that their life span was right truncated. For living individuals, however, current age was used so that their estimated life span was left-truncated because the actual value of life span would be greater because death would occur at a later age.

To compare the baseline characteristics for each ethnic group, we compared the ages in the parents and siblings of probands from the three ethnic groups. Because of non-independence among family members, we used generalized estimating equations to compare years of life span and to examine the frequency of health conditions among family members across ethnic groups by treating individuals within each family as a cluster [Zeger and Liang, 1986; Liang and Zeger, 1993].

We computed additive genetic heritability of life span using a maximum likelihood variance component model as implemented in SOLAR [Almasy and Blangero, 1998]. Heritability of life span was estimated as a proportion of the additive genetic variance over the total variance (genetic and environmental). Because families were ascertained through probands who were 65 years of age or older, we corrected for ascertainment by computing the likelihood conditional on the probands [Almasy and Blangero, 1998]. To adjust for the rapid increase in the life expectancy in the United States over the last 50 years, we carried out two separate analyses. First, we adjusted for cohort effect by categorized relatives into seven birth cohort groups based on their birth year. Each birth cohort was 20 years in duration, starting in 1820. Second, we restricted the heritability analysis to the proband's sibships as there would likely to be significant differences in the environment between the parent and proband generations. In addition to the cohort effect, we adjusted for sex as a covariate.

We repeated the heritability of survival within each ethnic group, stratified by the sex and then by the age of the proband. The rationale for the stratification based on proband sex is based on a liability model [Falconer, 1989]. This model assumes that there is a continuum of genetic risk that is normally distributed, and the phenotype is expressed when a threshold is exceeded. Because the life expectancy for men is lower than for women, male probands aged 65 years or older represent a more extreme end of the age distribution in the general population, and were considered a higher level on the liability scale than women. Similarly, we computed heritability stratified by age of proband (80 vs. <80 years) within each ethnic group, where the older probands may represent the higher level in the liability scale.

RESULTS

Compared with the African-American and Caucasian ethnic groups the number of Caribbean Hispanic probands was slightly larger (Table I). Among probands there were more women than men (68 vs. 32%), particularly in African-Americans. The mean age of probands did not differ across the ethnic groups (African-American 78.5 years, Caribbean Hispanic 78.0 years, and Caucasian (78.7 years) but women were consistently older than men (78.8 vs. 77.4 years). Hispanics had the largest number of siblings (5.2 per family), followed by African-Americans (4.0 per family) and by Caucasians (2.6 per family).

The mean years of life span for deceased relatives (both parents and siblings) was significantly younger for African-Americans (62.7 years), followed by Hispanics (64.4 years) and by Caucasians (65.6 years) (Table II). There were no differences in life span for deceased Hispanic and Caucasian parents of probands, and there were no differences between deceased African-American and Caucasian siblings. Combining those with known life spans and those whose life span was computed based on their current age showed a similar relation in which the survival age was lower for African-Americans and Caribbean Hispanics than Caucasians. While there were no differences in survival age of Hispanic and Caucasian parents of probands, there were significant differences between the ethnic groups when siblings were considered (Table II).

Heritability of Life Span

We initially computed heritability based on the variance decomposition model using two-generation pedigrees sepa-

TABLE I. Characteristics of Probands and Family Members Evaluated

Characteristics	Total[b]	African-Americans	Hispanics	Caucasians
Probands (number of families)	2,362	779	926	657
Male	749 (31.7%)	218 (28.0%)	286 (30.9%)	245 (37.3%)
Female	1,613 (68.3%)	561 (72.0%)	640 (69.1%)	412 (62.7%)
Relatives	13,161	4,201	6,216	2,744
Male	6,648 (50.5%)	2,102 (50.0%)	3,152 (50.7%)	1,394 (50.8%)
Female	6,513 (49.5%)	2,099 (50.0%)	3,064 (49.3%)	1,350 (49.2%)
Number of relatives by proband sex	13,161	4,201	6,216	2,744
Male probands	4,107 (31.2%)	1,150 (27.4%)	1,918 (30.9%)	1,039 (37.9%)
Female probands	9,054 (68.8%)	3,051 (72.6%)	4,298 (69.1%)	1,705 (62.1%)
Number of relatives by proband age[a]	12,980	4,116	6,134	2,730
≥80 years	5,352 (41.2%)	1,731 (42.1%)	2,423 (39.5%)	1,198 (43.9%)
<80 years	7,628 (58.8%)	2,385 (57.9%)	3,711 (60.5%)	1,532 (56.1%)

[a]Total number of relatives by proband age differs from the total number of relatives by proband sex because families with missing proband age were excluded.
[b]Percentages here refer to the total column.

rately within each ethnic group first by restricting the analysis to families in which both parents and siblings of the probands were deceased and total life span was known. Table IIIa shows unadjusted heritability estimates as well as heritability estimates adjusting for sex and birth cohort of relatives. As is apparent in Table IIIa, both the unadjusted and adjusted analyses heritability estimates for Caucasians and Caribbean Hispanics were statistically significant but neither result was significant for African-Americans. In fact, the estimate for African-Americans was quite low. We then computed heritability restricting to deceased siblings of the probands to minimize the potential cohort effect. Table IIIb shows that for Caucasians, both the crude and adjusted heritability was statistically significant; however, for African-Americans and Caribbean Hispanics, it was not significantly different from zero, although the heritability estimate increased.

Given that the heritability estimates were similar across ethnic groups for the proband-sibling generation but were different when both parents and sibs were considered, we compared the frequency of medical conditions among deceased family members across the three ethnic groups, as an attempt to explain the low heritability we observed for African-Americans. Among deceased relatives of African-Americans a history of stroke was significantly more frequent, but there was no significant difference in the reported frequency of Alzheimer's disease, Parkinson's disease, hypertension, or heart attack.

Heritability of Survival

We recomputed heritability using the survival age as described above (Table IIIc). Both the crude and adjusted (for sex and cohort) heritability estimates were statistically significant for African-Americans, Caribbean Hispanics, and Caucasians. In addition, we repeated the analysis adjusting for the presence of one or more chronic diseases in the proband (cancer, cardiovascular disease, diabetes, or hypertension), but the estimates did not change. We then restricted the analysis to the proband generation to minimize cohort effect (Table IIId), and all of the heritability estimates increased substantially. The unadjusted additive genetic heritability was 0.46 ($P = 1.0 \times 10^{-7}$) for Caucasians, 0.39 ($P = 1.0 \times 10^{-7}$) for African-Americans, and 0.37 ($P = 1.0 \times 10^{-7}$) for Hispanics. We included sex and birth cohort as covariates, and the heritability estimates were comparable across three ethnic groups. The adjusted heritability estimate was 0.38 ($P = 1.0 \times 10^{-7}$) for Caucasians, 0.35 ($P = 1.0 \times 10^{-7}$) for African-Americans, and 0.34 ($P = 1.0 \times 10^{-7}$) for Hispanics. We repeated the analysis adjusting for the presence of a chronic disease in the proband (cancer, cardiovascular disease, diabetes, or hypertension), the estimates did not change significantly.

To determine whether or not the proband's age predicted differential effects on heritability, we stratified families by proband age, ≥80 years and <80 years (Fig. 1). In African-Americans, relatives of older probands had a higher heritability estimate than relatives of younger probands (0.26 ($P = 2.5 \times 10^{-6}$) versus 0.10 ($P = 9.2 \times 10^{-4}$), respectively). Similarly, relatives of older Hispanic probands had a higher heritability estimate than relatives of younger Hispanic probands (0.18 ($P = 1.0 \times 10^{-7}$) versus 0.12 ($P = 1.0 \times 10^{-7}$), respectively). For Caucasians, however, relatives of older proband had lower heritability estimate than relatives of the younger probands (0.16 ($P = 7.9 \times 10^{-4}$) versus 0.28

TABLE II. Comparison of the Years of Total Life Span in Deceased and Living Family Members

Life span	N	African-Americans	N	Hispanics	N	Caucasians
Deceased						
Parents*	256	66.8	182	69.6	428	70.5
Siblings**	150	55.8	99	54.9	237	56.6
Combined***	406	62.7	281	64.4	665	65.6
Deceased and living relatives combined						
Parents[§]	1,164	70.7	1,386	74.1	1,208	72.7
Siblings***	1,810	62.6	2,863	64.6	1,278	66.6
Combined***	2,974	65.8	4,249	67.7	2,486	69.6

Comparisons were made using generalized estimating equations in which family membership was treated as a cluster before comparison across groups.
*African-American significantly lower than Hispanic and Caucasian, $P < 0.001$.
**Caucasians differ significantly from African-Americans and Hispanics, $P < 0.001$.
***All groups differ significantly from each other, $P < 0.001$.
[§]African-American significantly lower than Hispanic and Caucasian, $P < 0.001$.

TABLE III. Heritability of Life Span by Ethnic Group for Deceased Relatives and for Deceased and Living Relatives Combined

	African-Americans	Caribbean Hispanics	Caucasians
a: Life span of deceased parents and siblings of probands			
$h^{2\wedge}$	0.025 (0.00, 0.19)	0.195 (0.00, 0.44)	0.231 (0.10, 0.36)*
h^2 adjusted[a]	0.035 (0.017, 0.52)	0.288 (0.03, 0.54)*	0.261 (0.12, 0.39)*
b: Life span of deceased siblings (only) of probands			
$h^{2\wedge}$	0.220 (0.00, 0.55)	0.138 (0.00, 0.56)	0.551 (0.23, 0.87)*
h^2 adjusted[a]	0.160 (0.00, 0.48)	0.138 (0.00, 0.56)	0.421 (0.11, 0.74)*
c: Survival in parents and siblings of probands			
$h^{2\wedge}$	0.122 (0.06, 0.18)*	0.155 (0.16, 0.20)*	0.186 (0.11, 0.26)*
h^2 adjusted[a]	0.147 (0.08, 0.21)*	0.186 (0.13, 0.24)*	0.190 (0.13, 0.26)*
d: Survival in deceased and living siblings (only) of probands			
$h^{2\wedge}$	0.393 (0.25, 0.53)*	0.367 (0.26, 0.47)*	0.458 (0.28, 0.63)*
h^2 adjusted[a]	0.352 (0.22, 0.49)*	0.342 (0.24, 0.45)*	0.384 (0.21, 0.55)*

Heritability and 95% confidence intervals in parentheses.
[a]h^2 adjusted for age, sex, and birth cohort.
*$P < 0.001$.

($P = 1.0 \times 10^{-7}$), respectively). We also computed heritability after stratifying families by proband sex (Fig. 2). In Caucasians and Caribbean Hispanics, there were no significant differences in heritability estimates by proband sex. In African-Americans, the heritability estimate was lower in families of male probands than those of female probands.

DISCUSSION

Among first-degree relatives of elderly individuals from three ethnic groups living in three northern Manhattan communities in New York City, genetic influences on life span were estimated using two different methods. First, in deceased relatives of probands with known life spans, the genetic influence varied dramatically by ethnic group ranging from 0.29 to 0.26 for Caribbean Hispanics and Caucasians to as low as 0.04 for African-Americans. Restricting the analysis to probands and their siblings in the same generation increased the estimates of genetic influence substantially for Caucasians (0.42) and African-Americans (0.16), but not for Caribbean Hispanics (0.14). Second, we used survival combining the known life span from deceased relatives with current age in living relatives of the probands. The estimates increased for African-Americans, but not in Caribbean Hispanics or Caucasians. The degree genetic influence on survival age did not differ between the three ethnic groups, yielding the highest overall estimates of genetic influence, in the range of 0.34–0.38.

These findings confirm the modest degree of genetic influence on life span [Hrubec and Neel, 1981; Herskind et al., 1996; Kerber et al., 2001; Mitchell et al., 2001]. This study was focused on a representative sample of an elderly population 65 years of age or older from three ethnic groups in the United States, and not on twins, population (or cultural) isolates (e.g., the Amish or the Mormons in Utah), or an extreme sample (e.g., the New England centenarians). For most analyses, the estimated heritability of life span differed across the three ethnic groups, though the 95% confidence intervals suggest the differences were small. The most dramatic difference was in the analysis of life span in deceased relatives in which relatives of African-Americans showed little to no genetic variation in life span. Heritability estimates are influenced by all contributing components. When environmental contributions are large, heritability estimates will be low. Inequality between African-Americans and Caucasians in mortality and life expectancy has been described [Levine et al., 2001]. At age 16, life expectancy can vary as much as 28 years in these two ethnic groups [Geronimus et al., 2001]. Typically, total life expectancy from birth for African-Americans is consistently lower than for Caucasians [Minino and Smith, 2001]. In the

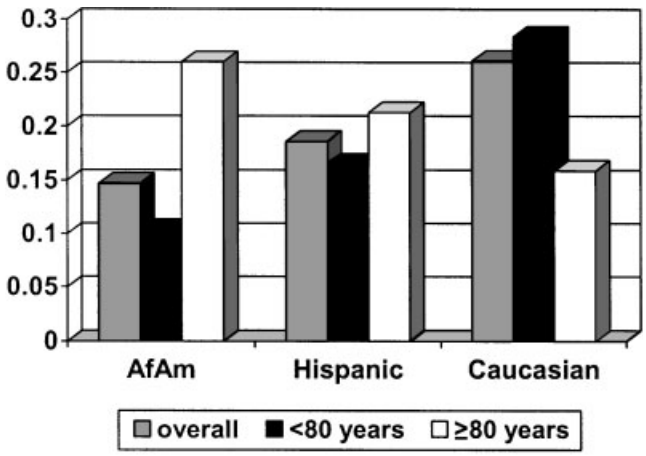

Fig. 1. This figure shows the adjusted heritability estimates for survival by ethnic group using parents and siblings of the probands, adjusting for sex and birth cohort. Within each ethnic group, heritability estimates stratified by proband age (≥80 years vs. <80 years) are also given.

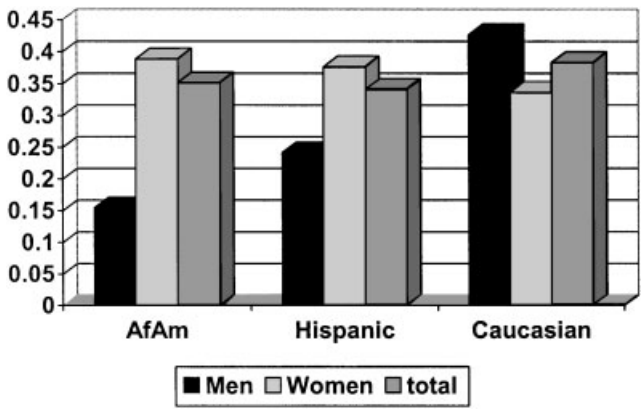

Fig. 2. This graph shows the heritability estimates for survival by ethnic group using siblings of the probands, adjusting for sex, and birth cohort. Within each ethnic group, heritability estimates stratified by proband sex are provided.

current study, the frequency of stroke was higher, but the prevalence of other health conditions was similar. It is possible that the broad influence of social disadvantage resulting in earlier mortality for a spectrum of health conditions and in increased all cause mortality may be related to the low heritability of life span in African-Americans.

Heritability estimates cannot distinguish the contributions of shared genes from shared environment. Parents, especially mothers, and their offspring share the same environment early in life. Siblings also share their childhood environment in addition for at least 50% of their genetic background. However, the shared environment decreases with age as family members begin to live apart from one another [Grilo and Pogue-Geile, 1991]. Heritability estimates are likely to be reasonable approximations of the genetic variance in life span, but they cannot apportion the degree of gene–environmental interaction.

While there were differences in the heritability of life span between ethnic groups, there were minimal ethnic differences in the heritability of survival. A number of factors could have contributed to this: (1) the ascertainment of probands who had already survived to age 65 or older, representing relatively healthy survivors; (2) difference between African-American and Caucasians in life expectancy after age 65 differs much less than at earlier ages; and (3) both have increased substantially and in parallel over the last decade [Minino and Smith, 2001]. In fact, Corti et al. [1999] found that before 80 years of age all cause mortality was higher in African-Americans than in Caucasians, but this relation completely reversed after age 80 years. Thus, by examining two different endpoints, life span and survival, we may be able to have a clearer understanding of the genetic influences on life span for minority populations.

We did not find a subgroup in our study with extremely high heritability of life span or survival age. We stratified by proband age, because having a proband with extreme age is a significant predictor of prolonged life span [Gudmundsson et al., 2000]. There was no significant difference in the heritability based on the age of the proband. Because life expectancy is lower for men than women, male probands surviving to 65 years of age or older are likely to represent the exception when compared with female probands. However, unlike other studies [Mitchell et al., 2001], heritability estimates did not differ significantly by sex.

Our study has limitations. The information on age and health status for relatives was obtained from probands who are 65 or older. To minimize the potential impact of misclassification we restricted our analysis to parents and siblings of probands, and called relatives when the information appeared inconsistent or unusual. The recall problem may become more serious for older compared with younger informants. However, there is no a priori reason to believe that informants will systematically over- or under-estimate their parent ages. Limited recall would lead to non-differential bias, favoring the null hypothesis of no differences in heritability. Although the ethnic categories include many heterogeneous groups, self-reporting of ethnic group provides a reasonable step in controlling for cultural, social, biological, and environmental differences [Risch et al., 2002].

The heritability of life span among twins is variable, ranging from 10% among twins reared apart to 50% among same sex twins [McGue et al., 1993; Ljungquist et al., 1998]. Using the Danish twin survival data, Yashin and Iachine [1995] observed that less than 50% of the variability in individual survival was determined by genetic factors. Sex differences in heritability are small and little change was noted in one study that considered three 10-year birth cohorts. Over the total age range, 30% of the variance in life span was attributable to genetic factors [Ljungquist et al., 1998]. Heritability of life span in the Old Order Amish has been estimated to be 25%. Parent and offspring ages at death were highly correlated, as were ages of death among siblings [Mitchell et al., 2001]. More importantly, the correlation coefficients for life span for parent–offspring pairs were remarkably similar to that among sibling pairs. Mitchell et al. [2001] argue that this reflects the similarity in environmental influences among the Amish, distinguishing this group from others. The strongest effects were found for parents and siblings surviving past the age of 75 years.

Gudmundsson et al. [2000], using the population-based genealogy in Iceland, found that the first-degree relatives of the probands who live to an extreme old age (95 centile) are twice as likely as the relatives of younger individuals to survive to the same age. The authors further assert that longevity is a heritable trait that is likely to be controlled by one or more genes, because familial risk $(\lambda - 1)$ decreases by a factor of two for each degree of relationship [Risch, 1990] and familial aggregation extends several generations in certain families.

Perls et al. [1998] compared siblings of individuals who did not survive past age 73 years with siblings of centenarians, and found that the siblings of centenarians were four times more likely to live to age 85 years or older. These individuals were also much healthier, and generally more active, than individuals 10–20 years younger [Perls et al., 1998, 2002]. Using a series of 137 families characterized by extreme longevity, defined as survival past the age of 98 years for at least one member of the family, Puca et al. [2001] found statistically significant evidence favoring linkage to a region on chromosome 4. Though a specific variant in a gene has not been identified, the finding of excess allele sharing in these families offers the opportunity to identify a gene that confers longevity.

Variant alleles in apolipoprotein E [Schachter et al., 1994; Lee et al., 2001; Rea et al., 2001], methylenetetrahydrofolate reductase [Brattstrom et al., 1998; Kluijtmans and Whitehead, 1999], and in MHC haplotypes have been inconsistently associated with longevity [Dubey et al., 2000; Lio et al., 2002]. Mutations in a gene encoding a helicase and exonuclease result in Werner's syndrome, a rare autosomal disorder causing progeria [Martin and Oshima, 2000]. Variant alleles at the Werner locus are not associated with aging in humans, however, but the nature and extent of the aging processes in Werner's syndrome may differ from normal aging [Martin, 1997; Martin and Oshima, 2000]. Mice without *Klotho*, a gene that encodes a type I membrane protein and shares homology with glycosides, age prematurely. Investigators have identified a polymorphism in the human *Klotho* gene on chromosome 13q12 that has been associated with longevity, defined as survival to age 75 years and older [Arking et al., 2002].

There can be little doubt that one's life span reflects their genetic background and the cumulative effects of both individual behavior and environmental factors. The search for genetic variants that influence total years of life is already in progress. The identification of the genetic contribution to life span will provide insight into molecular pathways that determine survival. Understanding these pathways will prove essential to unraveling the complex biology of aging. Given the modest heritability of life span, the lack of consistency in analyses of candidate genes tested thus far and the inherent difficulties of human compared to animal studies, characterization of endophenotypes that are strongly heritable and at the same time contribute significantly to the aging process becomes a priority.

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