Evolution, Mutations, and Human Longevity: European Royal and Noble Families

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Abstract The evolutionary theory of aging predicts that the equilibrium gene frequency for deleterious mutations should increase with age at onset of mutation action because of weaker (postponed) selection against later-acting mutations. According to this mutation accumulation hypothesis, one would expect the genetic variability for survival (additive genetic variance) to increase with age. The ratio of additive genetic variance to the observed phenotypic variance (the heritability of longevity) can be estimated most reliably as the doubled slope of the regression line for offspring life span on paternal age at death. Thus, if longevity is indeed determined by late-acting deleterious mutations, one would expect this slope to become steeper at higher paternal ages. To test this prediction of evolutionary theory of aging, we computerized and analyzed the most reliable and accurate genealogical data on longevity in European royal and noble families. Offspring longevity for each sex (8409 records for males and 3741 records for females) was considered as a dependent variable in the multiple regression model and as a function of three independent predictors: paternal age at death (for estimation of heritability of life span), paternal age at reproduction (control for parental age effects), and cohort life expectancy (control for cohort and secular trends and fluctuations). We found that the regression slope for offspring longevity as a function of paternal longevity increases with paternal longevity, as predicted by the evolutionary theory of aging and by the mutation accumulation hypothesis in particular.

The evolutionary theory of aging predicts that the equilibrium gene frequency for deleterious mutations should increase with age at onset of mutation action

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because of weaker (postponed) selection against later-acting mutations (Medawar 1946, 1952; Finch 1990; Rose 1991; Partridge and Barton 1993; Charlesworth 1994). According to this mutation accumulation hypothesis, one would expect the genetic variability for survival (additive genetic variance) to increase with age (Partridge and Barton 1993; Charlesworth 1994). In general, both the additive genetic component of variance and the dominant component are expected to increase with age under the mutation accumulation hypothesis (because for traits affected by rare deleterious alleles, both components increase with increasing mutant allele frequency) (Charlesworth 1987; Falconer 1989; Hughes and Charlesworth 1994). The ratio of additive genetic variance to the observed phenotypic variance (the heritability of longevity) can be estimated most reliably as the doubled slope of the regression line for offspring life span on paternal age at death (the regression of offspring on mothers sometimes gives too high an estimate because of maternal effects, as it would, for example, with body size in most mammals) (Falconer 1989). That is why the slope of the regression line on *paternal* age at death was used in this study as an estimate for heritability of human longevity. Thus, if longevity is indeed determined by late-acting deleterious mutations, one would expect this slope to become steeper at higher paternal ages (Gavrilova et al. 1997). The purpose of this brief communication is to report the preliminary results of a test of this prediction of the evolutionary theory of aging and of the mutation accumulation hypothesis in particular.

Materials and Methods

In this study the most reliable and accurate existing data on human familial longevity were collected, computerized, and analyzed: the genealogical data on longevity in European royal and noble families published in Van Hueck's *Genealogisches Handbuch des Adels* (1980, 1985, 1986, 1987, 1988, 1991, 1992, 1993, 1994) and in other professional genealogical sources listed elsewhere (Gavrilov et al. 1996). These data were chosen to minimize the social heterogeneity of the population under study and to avoid overstating the familial component of longevity when a mixture of families with different social statuses is analyzed. Thus, although the sample analyzed in this study is biased toward higher social status and does not represent the whole human population, it is the best possible sample where the effects of population heterogeneity are minimized with regard to social status.

Offspring longevity was analyzed for adults (those who survived by age 30) to study the effects of late-acting mutations. The data for offspring born in the twentieth century were excluded from the analysis so that the estimates of longevity for extinct birth cohorts were unbiased. The data for offspring born before the nineteenth century were also excluded to minimize the heterogeneity of the population.

Table 1. Heritability of Human Longevity (One-Half) as a Function of Paternal Age at Death

Paternal Age at Death (Years)	*Regression Slope ± Standard Error for Offspring Life Span[a] on Paternal Age at Death*	
	Daughters (Sample Size)	*Sons (Sample Size)*
30+	0.10 ± 0.02 (3741)	0.09 ± 0.01 (8409)
40+	0.12 ± 0.02 (3643)	0.10 ± 0.01 (8173)
50+	0.13 ± 0.03 (3361)	0.10 ± 0.02 (7454)
60+	0.15 ± 0.04 (2688)	0.12 ± 0.02 (5966)
65+	0.23 ± 0.05 (2177)	0.15 ± 0.03 (4879)
70+	0.29 ± 0.06 (1652)	0.17 ± 0.04 (3656)
75+	0.52 ± 0.09 (1103)	0.33 ± 0.06 (2456)

a. Life span is calculated for adults (those who survived by age 30).

For each birth cohort the sex-specific mean expectation of life at age 30 was calculated and used as a dependent variable in a multiple linear regression to control for cohort and secular effects on human longevity. Offspring longevity for each sex (8409 records for males and 3741 records for females) was considered a dependent variable in the multiple regression model (program 1R in the BMDP statistical package) and a function of three independent predictors: (1) paternal age at death (for estimation of heritability of life span), (2) paternal age at reproduction [a control for parental age effects, because recent studies have demonstrated that daughters born to older fathers live shorter lives (Gavrilov et al. 1996, 1997; Gavrilov and Gavrilova 1997a,b)], and (3) sex-specific cohort life expectancy (a control for cohort and secular trends and fluctuations in life span).

The F ratio for each multiple regression was higher than 17.0, and all the regressions were statistically highly significant ($p < 0.0001$).

Results

The heritability of human longevity is 18% ± 2% for sons (regression slope 0.09 ± 0.01) and 20% ± 4% for daughters (regression slope 0.10 ± 0.02) born to fathers who lived 30 years or more (Table 1). At advanced paternal ages heritability estimates are much higher: 34% ± 8% for sons (regression slope 0.17 ± 0.04) and 58% ± 12% for daughters (regression slope 0.29 ± 0.06) born to fathers who lived 70 years or more (Table 1). It is worth noting that the heritability estimates were higher in daughters than in sons at all paternal ages, although this gender gap is statistically significant only at advanced paternal ages.

The higher heritability of longevity for daughters might be explained by their specific inheritance of the paternal X chromosome, which is richer in genetic information than the small paternal Y chromosome inherited by sons (Gavrilov and Gavrilova 1991, 1994).

Discussion

Our results demonstrate a significant increase in heritability of human longevity at advanced parental age at death (above age 60), predicted by the evolutionary theory of longevity and by the mutation accumulation hypothesis in particular. In fact, this observation is paradoxical because it is well known that there is strong selection against deleterious mutations and that by older ages most of such mutations should have been selected out. That is why one would expect an age-dependent decrease in heritability of human longevity rather than the increase in heritability found here. The fact that, despite strong selection against deleterious mutations, there is still significant genetic heterogeneity in the population with regard to longevity is remarkable. It should be noted, however, that the evolutionary theory of aging and the mutation accumulation theory are not the only possible explanations for the observed age-related increase in familial resemblance for longevity.

One of the alternative explanations of the observed phenomenon was proposed by one of the anonymous reviewers of this brief communication: Those persons who have parents that live long lives may have more similar environments, and those who have parents who die at an early age may have more variable social environments depending on other social situations. If this is the case, then the age-related increase in heritability estimates may be due to a decrease in environmental variation rather than to an increase in genetic variability. This may result in higher familial resemblance in longevity for those who have long-lived parents. This hypothesis could be tested through an analysis of longevity variance, because the hypothesis predicts that the observed total phenotypic variance for longevity of those born to long-lived parents should be less compared with those born to short-lived parents. Our analysis demonstrates, however, that the observed variance is essentially the same for all compared groups (standard deviation for longevity of the offspring surviving by age 30 is 14–15 years) and is not related to parental longevity. Thus the observed age-related increase in familial resemblance for human longevity could not be explained simply by the decrease in the environmental component of variance only. Further studies in this direction for larger sample sizes and other data sets are planned to clarify this issue.

Another interesting implication of the obtained results is the explanation of the longevity paradox: Although the heritability estimates for longevity have been reported to be rather low (Murphy 1978; Wyshak 1978; McGue

et al. 1993), it is also well known that cases of extreme longevity have strong familial association (Pearl 1931; Pearl and Dewitt 1934). This paradox could be explained by the present observation that heritability for human longevity is low only when it is studied in the wide age range but that heritability for longevity is rather high when estimated for long-lived parents (see Table 1).

The results presented here indicate that the familial component of human longevity was probably understated in previous studies, particularly in the case of longer lived parents. Further studies in this direction on larger sample sizes and other data sets (for comparative analysis) are planned because they could result in significant progress in understanding the mechanisms of familial transmission of human longevity.

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Literature Cited

Charlesworth, B. 1987. The heritability of fitness. In *Sexual Selection: Testing the Alternatives*, J.W. Bradbury and M.B. Andersson, eds. Chichester, England: Wiley, 21–40.

Charlesworth, B. 1994. *Evolution in Age-Structured Populations.* Cambridge, England: Cambridge University Press.

Falconer, D.S. 1989. *Introduction to Quantitative Genetics.* London, England: Longman.

Finch C.E. 1990. *Longevity, Senescence, and the Genome.* Chicago, IL: University of Chicago Press.

Gavrilov, L.A., and N.S. Gavrilova. 1991. *The Biology of Life Span: A Quantitative Approach.* New York: Harwood Academic.

Gavrilov, L.A., and N.S. Gavrilova. 1994. Sex and longevity. *Nature* 367:520.

Gavrilov, L.A., and N.S. Gavrilova. 1997a. Parental age at conception and offspring longevity. *Rev. Clin. Gerontol.* 7:5–12.

Gavrilov, L.A., and N.S. Gavrilova. 1997b. When fatherhood should stop? *Science* 277:17–18.

Gavrilov, L.A., N.S. Gavrilova, G.N. Evdokushkina et al. 1996. Determinants of human longevity: Parental age at reproduction and offspring longevity. *Longevity Rep.* 10(54):7–15.

Gavrilov, L.A., N.S. Gavrilova, V.N. Kroutko et al. 1997. Mutation load and human longevity. *Mutation Res.* 377:61–62.

Gavrilova, N.S., L.A. Gavrilov, Yu.E. Kushnareva et al. 1997. Testing the evolutionary theory of longevity. In *Aging beyond 2000: One World, One Future,* G.R. Andrews, ed. Bedford Park, Australia: 1997 World Congress of Gerontology Inc., 550.

Hughes, K.A., and B. Charlesworth. 1994. A genetic analysis of senescence in *Drosophila. Nature* 367:64–66.

McGue, M., J.W. Vaupel, N. Holm et al. 1993. Longevity is moderately heritable in a sample of Danish twins born 1870–1880. *J. Gerontol.* 48:B237–B244.

Medawar, P.B. 1946. Old age and natural death. *Mod. Q.* 2:30–49. [Reprinted in *The Uniqueness of the Individual,* by P.B. Medawar (New York: Basic Books, 1958), 17–43.]

Medawar, P.B. 1952. *An Unsolved Problem in Biology.* London, England: H.K. Lewis. [Reprinted in *The Uniqueness of the Individual,* by P.B. Medawar (New York: Basic Books, 1958), 44–70.]

Murphy, E.A. 1978. Genetics of longevity in man. In *The Genetics of Aging,* E.L. Schneider, ed. New York: Plenum Press, 261–301.

Partridge, L., and N.H. Barton. 1993. Optimality, mutation, and the evolution of aging. *Nature* 362:305–311.

Pearl, R. 1931. Studies on human longevity. IV. The inheritance of longevity—preliminary report. *Hum. Biol.* 3:245–269.

Pearl, R., and R. Dewitt. 1934. Studies on human longevity. VI. The distribution and correlation of variation in the total immediate ancestral longevity of nonagerians and centenarians, in relation to the inheritance factor in duration of life. *Hum. Biol.* 6:98–222.

Rose, M.R. 1991. *Evolutionary Biology of Aging.* Oxford, England: Oxford University Press.

Van Hueck, W., ed. 1980–1994 (various years). *Genealogisches Handbuch des Adels.* Limburg an der Lahn, Germany: C.A. Starke Verlag.

Wyshak, G. 1978. Fertility and longevity of twins, sibs, and parents of twins. *Soc. Biol.* 25:315–330.