

Evolution of human longevity and the genetic complexity governing aging rate*

(primates/hominids/cranial capacity/body weight)

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ABSTRACT Genetic complexity of processes governing the aging rate of man was estimated by determining the maximum rate lifespan has evolved along the hominid ancestral-descendant sequence. Maximum lifespan potential was found to have increased approximately 2-fold over the past 3 million years, reaching a maximum rate of increase of 14 years per 100,000 years about 100,000 years ago. It is estimated that about 0.6% of the total functional genes have received substitutions leading to one or more adaptive amino-acid changes during this 100,000-year time-period. This suggests that aging is not the result of an expression of a large number of independently acting processes. Instead, primary aging processes appear to exist where only a few genetic changes are necessary to decrease uniformly the aging rate of many different physiological functions.

Maximum lifespan (MLS) potential is defined as the maximum observed lifespan of a species (1-3). This value is usually obtained with animals living under favorable conditions but does not vary greatly even over a wide range of living conditions. There is about a 50-fold range of MLS potential for the mammalian species (1-4). However, the various types of age-dependent physiological dysfunctions and diseases are quite similar and are expressed in similar temporal patterns. This is not surprising, considering the similarities at the physiological, biochemical, and molecular levels for the mammalian species, and particularly for the primates, where a 10- to 12-fold difference in MLS potential is found (5-7). Thus, mammalian species appear to age qualitatively in the same manner, by the same types of biological processes, but at different rates that can vary over a 50-fold range (3, 8-10).

These types of observations had suggested that the genetic processes governing aging rate may not be too complex (8, 11, 12). However, there are other arguments that suggest that the aging process is highly diverse and complex, involving many different genes acting independently of one another (13-18). If this were true, then a uniform increase in lifespan, maintaining the qualitative aspects of the aging process, would require a change in all of these genes.

In this paper, the genetic complexity of the processes governing aging rate in man is estimated by determining the highest rate at which MLS potential has evolved along the hominid ancestral-descendant sequence leading to modern man. This rate is compared to the range of evolutionary rates of other characteristics of mammals and to estimates of the maximum rate new genes could have evolved during this time period.

Abbreviations: MLS, maximum lifespan; yr, year.

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RESULTS

Prediction of maximum lifespan potential and developmental rate

MLS potential can be predicted for most mammalian species with an accuracy of about 25% by use of the multiple allometric regression of lifespan on brain weight and body weight developed by Sacher (1, 19). This is illustrated in Table 1, where a comparison is made between observed and predicted MLS potentials for representative primate species of Old World monkeys, apes, and man. There is also an excellent correlation between the relative time period required to reach various stages of development and the MLS potential of these primates (20). A ratio of about five is found between MLS potential and the time period required to reach sexual maturity for the higher-ordered primate species.

Estimation of maximum lifespan potential for the hominids

The prediction of MLS potential for the primate species is equally good for the different "grades" of primate species (i.e., the living fossil-like species in Prosimii as compared to man) (1, 3, 19). In addition, the hominid species are expected to have similar biological characteristics, and therefore similar aging processes, as observed in the primates, particularly between chimpanzee and modern man (7). Therefore, it is reasonable to expect that the prediction of MLS potential by the Sacher equation should also apply to the fossil hominid species.

The estimates of cranial capacities and body weights of species generally believed to be part of the ancestral-descendant sequence of hominid evolution are shown in Table 2 with their corresponding estimates of date of appearance. Approximately a 2-fold increase in MLS potential is predicted to have occurred over the last 3 million years of hominid evolution.

Estimates of the age at death for a few of these hominid species were available and are shown in Table 2. These estimates are all substantially smaller than the predicted MLS potentials. The values, however, are not likely to represent MLS potential and would, therefore, be expected to be smaller. The method used to estimate the age at death is based on the assumption that the bone and tooth developmental rates in the hominids are similar to those in modern man (38, 42). This procedure may result in an important underestimation of the actual age at death for these hominids (3, 19). In Table 1, it was shown that a constant ratio exists between sexual maturation age and MLS potential for the higher-ordered primates. This relation was used in Table 2 to predict the sexual maturation age for the hominids. The

Table 1. Comparison between observed and predicted maximum lifespan potentials and developmental rates for some Old World monkeys, apes, and man

Genus and species	Common name	(Sex)	Body wt. ^a (g)	Cranial capacity ^a (cm ³)	Lifespan (yr)		Sexual maturation age (yr)	
					Observed ^b	Pre-dicted ^c	Observed ^d	Predicted ^e
<i>Presbytis entellus</i>	Langur	(♂)	21,000	120	22	24	3-4	4-5
<i>Macaca mulatta</i>	Rhesus macaque	(♂)	6,000	90	29	27	4-5	5-6
<i>Papio cynocephalus</i>	Western baboon	(♂)	22,000	200	32	35	5-6	6-7
<i>Hylobates lar</i>	Gibbon	(♂)	5,500	100	32	30	7-8	6-7
<i>Pongo pygmaeus</i>	Orangutan	(♂)	69,000	420	50	41	9-10	8-9
<i>Gorilla gorilla</i>	Gorilla	(♂)	140,000	555	40	42	8-9	8-9
<i>Pan troglodytes</i>	Chimpanzee	(♂)	38,500	410	45	46	8-9	8-9
<i>Homo sapiens</i> modern	Man	(♂)	65,000	1,450	95	92	17-18 ^f	17-18
		(♀)	58,000	1,330		89		

^a These values are considered typical of the species and are from Schultz (20), Tobias (21), Jerison (22), and Stephan *et al.* (23). Most are rounded off to avoid appearance of high accuracy.
^b Jones (24, 25), *Biology Data Book* (26), and Napier and Napier (27).
^c Maximum lifespan values (MLS) were calculated from the Sacher equation (1): $MLS = (10.83) (\text{Brain wt., g})^{0.636} (\text{Body wt., g})^{-0.225}$. Differences in cranial capacity (cm³) and brain wt. (g) are considered negligible for these calculations (23).
^d Schultz (20) and Napier and Napier (27).
^e Predicted from the equation: Sexual maturation age = (0.2) (MLS). This relation was experimentally determined for the higher-ordered primate species.
^f Eighteen years is best estimate of sexual maturation about 200 years ago. It has since decreased from this value to 13.5 yr (28).

results suggest that the general developmental rate was not constant, but steadily decreased with time along the hominid ancestral-descendant sequence.

The predicted MLS potential along the ancestral-descendant sequence of the hominids is shown in Fig. 1. It is found

to increase steadily, reaching a maximum about 100,000 years ago, and then to remain essentially constant up to the present time. The MLS potentials and times of appearance of the hominid species were found to correspond closely to a linear relation (between 4 million and 100,000 years ago)

Table 2. Estimate of maximum lifespan potential and developmental rate for the hominids from fossil body weight and cranial capacity measurements

No.	Genus and species	Body weight (kg)		Cranial capacity (cm ³)		Time of appearance ^a (yr × 10 ⁻⁶)	Maximum lifespan (yr)		Predicted sexual maturation age (yr) ^f
		Measured ^a	Pre-dicted ^b	Measured ^a	Pre-dicted ^c		Observed ^d	Pre-dicted ^e	
1	<i>Ramapithecus punjabicus</i>	32	—	300	280	14	—	42	8-9
2	<i>Australopithecus africanus</i>	32	32	450	460	3	35-40	51	10-11
3	<i>Australopithecus robustus</i>	40.5	—	500	490	2.5	35	52	10-11
4	<i>Australopithecus boisei</i>	47.5	—	530	530	2	—	52	10-11
5	<i>Homo habilis</i>	43	45.3	660	580	1.5	—	61	12-13
6	<i>Homo erectus javanicus</i>	53	52.3	860	740	0.7	40-60	69	13-14
7	<i>Homo erectus pekinensis</i>	53	56.3	1040	1030	0.25	40-60	78	15-16
8	<i>Homo europaeus pre-Würm</i>	—	57.6	1310	1380	0.1	40-60	89	17-18
9	<i>Homo neanderthalensis europaeus</i>	—	58.1	1460	1500	0.045	40-60	93	18-19
10	<i>Homo sapiens europaeus Würm</i>	—	58.4	1460	1480	0.015	—	94	18-19
11	<i>Homo sapiens recens</i>	—	58.4	1460	1480	0.01	90	94	18-19
12	<i>Homo sapiens modern</i>	63.5	58.5	1410	1360	present	95	91	18-19

^a Mean body weight estimates are taken from recent values based on fossil data (29-32), brain to body weight allometric relationships (33, 34), and a comparative basis (29, 33). Mean cranial capacity measurements for the hominid species were taken from the fossil data analyzed by Tobias (21), Parenti (35), and Pilbeam and Gould (33). Estimates are rounded off to avoid appearance of high accuracy. Some of the estimates are quite accurate and others only educated guesses. However, most values and times of appearance are considered to be accurate within 20%.

^b A near linear relationship was found between body weights of *A. africanus*, *H. habilis*, and *H. erectus* and time of appearance (3). Using this relationship, body weights were predicted when values were not available. Close agreement of the predicted body weights with the independently measured weights indicates that these predictions, where the measured values are not available, are reasonable.

^c Predicted values of hominid cranial capacities were from two equations derived from a large number of fossil data presented by Lestrel and Read (36). These are: Brain wt. (g) = 55,745 (time)^{-0.32} for time = 4 × 10⁶ to 1.6 × 10⁵ yr. (This equation represents my derivation from their data, and brain wt. (g) = 1321 (time)^{0.012} for time = 1.6 × 10⁵ to 10 yr.) Close agreement of the independently measured cranial capacities with the predicted capacities indicates that these values are reasonable.

^d Based on fossil evidence (37-40) and survival time in primitive societies (41).

^e From Sacher equation given in footnote in Table 1.

^f From mean ratio of maximum lifespan to sexual maturation time of 5.0 (see Table 1 footnote).

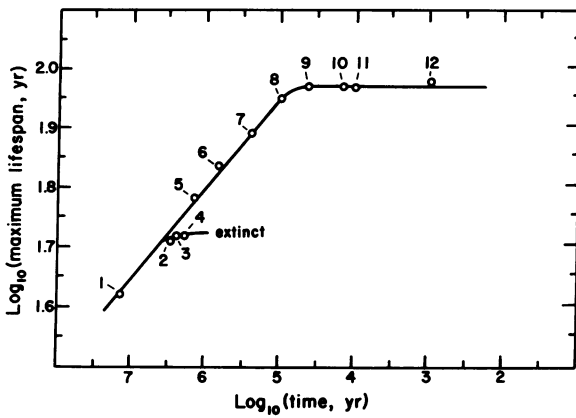


FIG. 1. Relationship between MLS potential and time of appearance of the hominid species. Numbers indicate genus and species of hominids listed in Table 2.

when plotted on log versus log coordinates. This relation was used to obtain an estimate of the rate of increase in MLS potential.

The similar MLS potentials for the gracile species *A. africanus* and the more robust species *A. robustus* and *A. boisei* suggest that a divergence occurred in the hominid lineage about 3–4 million years ago. It appears as if the robust species later became extinct. The absence of an increase in MLS potential along this lineage may have played an important role in the evolutionary failure of such new races.

Rate of increase of maximum lifespan potential

Estimates of the rate of increase in MLS potential are shown in Table 3. The rate steadily increased, reaching a maximum

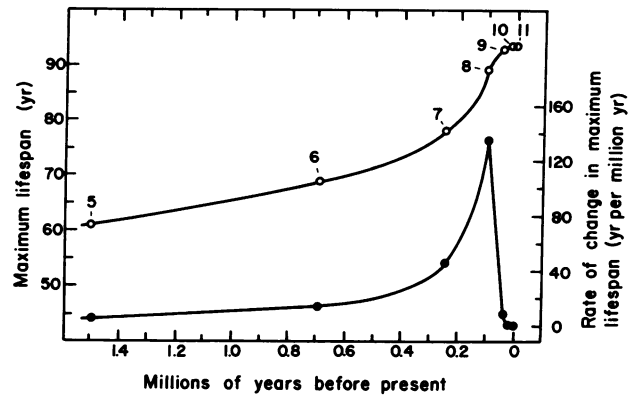


FIG. 2. Rate of increase in MLS potential along the ancestral-descendant sequence of the hominids leading to modern man. Numbers indicate genus and species of hominids listed in Table 2. (O), maximum lifespan, yr; (●), rate of change in MLS potential, yr per million yr.

value of 140 years per million years approximately 100,000 years ago with the appearance of *Homo europaeus* pre-Würm and then rapidly decreased to zero. These results are shown in Fig. 2.

The nucleotide substitutions occurring during evolution are expected to have a wide range of effects. Although these changes have frequently been classified as being either deleterious, neutral, or advantageous, there is likely to be a continuous gradient of effects between these extremes (45–47). The mean rate of change in nucleotide pairs per genome along the ancestral-descendant sequence of the hominids since the divergence of the chimpanzee to the present time has been estimated to be 0.08% per million years according to fossil dating and 0.22% per million years according to al-

Table 3. Estimates of the evolutionary rate of increase in maximum lifespan potential along the ancestral-descendant sequence of the hominids leading to modern man

No.	Genus and species	Rate of increase of MLS potential (yr per 10 ⁶ yr) ^a	Change in MLS potential per percent change in nucleotide pairs ^b	Rate of increase in MLS potential in millidarwin units ^c
1	<i>Ramapithecus punjabicus</i>	0.5	2	4
2	<i>Australopithecus africanus</i>	3	14	22
3	<i>Australopithecus robustus</i>	2	9	14
4	<i>Australopithecus boisei</i>	0	0	0
5	<i>Homo habilis</i>	6	27	36
6	<i>Homo erectus javanicus</i>	14	64	75
7	<i>Homo erectus pekinensis</i>	47	210	220
8	<i>Homo europaeus</i> pre-Würm	140	640	580
9	<i>Homo neanderthalensis europaeus</i>	10	45	40
10	<i>Homo sapiens europaeus</i> Würm	0	0	0
11	<i>Homo sapiens recens</i>	0	0	0
12	<i>Homo sapiens</i> modern	0	0	0

^a Equation describing linear relationship shown in Fig. 1 between MLS potential and time of presence of a given hominid species is calculated as:

$$MLS = (518.8) t^{-0.153} \text{ for } t = 10^7 \text{ to } 0.1 \times 10^6 \text{ yr}$$

where the rate of increase of MLS (yr) per 10⁶ yr is calculated from the equation:

$$\frac{dMLS}{dt} = (79.37) t^{-1.153}$$

^b Based on a mean value of 0.22% change in nucleotide sequences per genome per million years according to fossil dates along the ancestral-descendant sequence of the hominids leading to modern man, beginning with the divergence of the chimpanzee (43).

^c Evolutionary rate in darwin units is calculated as (44):

$$d = \frac{dMLS}{dt} \cdot \frac{10^6}{MLS} \cdot \frac{1}{e}$$

where *e* is the base of natural logarithms and is defined as one darwin unit.

bumin dating (43). These values represent the resultant fixation rate of all nucleotide pair changes occurring during hominid evolution (except those that are deleterious). The extent MLS potential changed with respect to these nucleotide substitutions is shown in Table 3 and indicates that a maximum increase of 6.4 years occurred per 0.01% change in nucleotide pairs.

Estimates of the evolutionary rate of increase in MLS potential in terms of darwins (44) are in Table 3. The darwin represents a rate of evolutionary change normalized with respect to the parameter being measured and is useful in comparing the evolutionary rate of other characteristics of animals during the course of their evolution. A maximum value of about 580 millidarwins for MLS potential is calculated with the appearance of *Homo europaeus* pre-Würm, approximately 100,000 years ago. Typical rates of evolution of many different characteristics for mammals are in the range of 30 millidarwins (48).

DISCUSSION

An average increase in MLS potential of approximately 2-fold was found to have occurred over the past 3 million years along the hominid-ancestral descendant sequence. During this period, MLS potential increased and reached a maximum rate of 14 years per 100,000 years with the appearance of *Homo europaeus* pre-Würm, 100,000 years ago. An average increase of about 10 years in MLS potential or a 12.5% decrease in aging rate occurred between 200,000 and 100,000 years ago.

This 100,000-year time-period is used below to estimate the genetic complexity involved in governing the aging rate of the hominids. At the beginning and end of this interval, it is assumed that the qualitative spectra of aging processes are similar among the two populations of hominid species. To achieve this, it is assumed that most of the genes involved in governing aging rate are modified during this time period. However, because of the similarity of the aging processes among all the primate species, it is likely that the genes modified during this 100,000-year period were the same at all stages of non-primate and hominid evolution (3, 10).

An upper limit to the number of genes governing the aging processes of the hominids can be determined from an estimate of the maximum number of genes which could have had one or more advantageous substitutions fixed during the 100,000-year time-period. This has been done using three different methods.

Haldane (49) has estimated that the maximum rate of adaptive gene substitution in mammalian evolution could not be more than one substitution per genome per 300 generations. Although this estimation has been accepted by Kimura and Ohta (50), it has been questioned and may possibly be an order of magnitude too low (51, 52). It is generally agreed that the maximum number of genes per genome for mammals could not exceed 4×10^4 (45, 53, 54). With this gene number and Haldane's estimate, the fixation rate is calculated to be 10^{-7} AA/gene per generation (AA in amino-acid substitutions). This value is equivalent to 10^{-3} AA/gene per 10^4 generations (10^4 generations in a 10^5 -year period, assuming a generation time of 10 years). Assuming an even distribution of adaptive base substitutions along the genome, this rate predicts that on the average about 40 genes or 0.1% of the total functional genes received base substitutions leading to one or more adaptive amino-acid changes. This estimation method was also employed by Sacher (19).

The average rate that nucleotides have been fixed since

the divergence of chimpanzee and man has been estimated, using a DNA hybridization technique, to be 0.08% according to fossil dates (43). Assuming an average gene size of 1000 nucleotide pairs and that substitution is evenly distributed along the genome, this value is equivalent to 6×10^{-2} AA/gene per 10^4 generations. A similar calculation for the average amino-acid substitution rate for a number of different proteins in mammals (including primates) gives a value of about 4.8×10^{-2} AA/gene per 10^4 generations (45, 47). The amino-acid fixation rate may, however, be substantially lower during recent hominid evolution if it has continued to decrease, as some data have indicated (43, 55, 56). For example, studies based on human and chimpanzee globins give 2 to 4×10^{-3} AA/gene per 10^4 generations between *Australopithecus* and modern man (56). It therefore appears reasonable to assume that the rate of fixation of nucleotides over the entire genome during recent hominid evolution did not exceed the equivalent of 6×10^{-2} AA/gene per 10^4 generations. This base fixation rate includes a broad and continuous spectrum of substitutions ranging from highly advantageous through completely neutral (including nonfunctional DNA) to a few even being slightly disadvantageous (46). Ohta and Kimura (57) have suggested 10% as an upper limit for adaptive substitutions. Using this estimate gives an adaptive fixation rate of about 6×10^{-3} AA/gene per 10^4 generations. Assuming 4×10^4 genes per genome, it is predicted that about 250 genes or 0.6% of the total functional genes have received base substitutions leading to one or more adaptive amino-acid changes in 10,000 generations of hominid evolution.

It is also possible theoretically to calculate the rate of evolution of adaptive gene substitutions (50, 58). N_e is taken to be 10^4 [about 0.95 of the true population (58)], μ to be 10^{-9} AA/gene per generation [equivalent to about one advantageous mutation per 100,000 (45, 59)], and s to be 10^{-2} (a moderately advantageous selective coefficient). These parameters give an adaptive fixation rate of 4×10^{-3} AA/gene per 10^4 generations. Assuming an even distribution and 4×10^4 genes per genome as before, this rate predicts that about 160 genes or 0.4% of the total functional genes received base substitutions leading to one or more amino-acid changes.

These calculations suggest that two of the most complex features of man, longevity and intelligence, evolved extremely rapidly with surprisingly few point mutational changes occurring in the genome (3, 11, 19). Other data have been reported suggesting relatively simple changes at the genetic level to account for complex phenotypic changes (53, 54, 60). A particularly interesting suggestion is that changes in the genetic regulatory system by gene rearrangement may be a major process in the evolutionary development of the primates (7, 61-63).

According to these arguments and the data presented in this paper, the aging process in mammals might also be controlled at the gene regulatory level and not by changes in the amino-acid sequence of structural proteins. Thus, genetic regulatory changes of structural genes already present may be able to decrease uniformly the rate of expression of most mammalian aging processes.

Some support for this model has been reported (3, 9, 10, 12). The most significant in this respect is the correlation found between the extent of UV excision repair and MLS potential in a wide range of mammalian species (64). Recent evidence has indicated that this difference might be simply a result of different synthesis rates of similar repair enzyme(s) (65).

If the information stability of DNA proves to be a major factor governing aging rate (9, 66), then an interesting prediction of these results is that mutation rate, acting as a primary aging process, may have actually decreased during the evolution of the primates. Other data have also indicated a decrease in mutation rate, and several explanations have been suggested (43, 47, 55, 56, 67). One common explanation is that this effect might be the direct result of an increased generation time (43, 67). The answer may in fact be the reverse: that an increased generation time was the result and not the cause of the decrease in mutation rate (3, 11).

After this paper was completed, I learned that George Sacher has estimated the MLS potential during hominid evolution by the allometric regression method (11, 19). He also found a high rate of increase of longevity and inferred that this may have been accomplished by allelic substitution at a comparatively small number of loci. I am happy to acknowledge the encouragement received from George Sacher and the stimulating discussions with Dr. R. W. Hart and John Wulf. This research was supported by the following granting agencies: Biomedical Sciences Support Grant RR-07133 from the General Research Support Branch, Division of Research Resources, National Institutes of Health; The University of Texas at Dallas Research Fund; the Yarborough and Associates Research Fund; and the Glenn Foundation for Medical Research.

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