Genetics of Aging

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The role of genetics in determining life-span is complex and paradoxical. Although the heritability of life-span is relatively minor, some genetic variants significantly modify senescence of mammals and invertebrates, with both positive and negative impacts on age-related disorders and life-spans. In certain examples, the gene variants alter metabolic pathways, which could thereby mediate interactions with nutritional and other environmental factors that influence life-span. Given the relatively minor effect and variable penetrance of genetic risk factors that appear to affect survival and health at advanced ages, life-style and other environmental influences may profoundly modify outcomes of aging.

Genes exert strong controls on life-span and patterns of aging. Yet we know little of how humans live five times longer than cats, cats live five times longer than mice, and mice live 25 times longer than fruit flies (*1*, *2*) or why the onset of Alzheimer's disease (AD) often differs by many years in identical twins. Equally obscure is the role of genetics in the unprecedented increases of human life expectancy at advanced ages (*1*). To approach these puzzles, we must understand how the potential life-span of an individual is determined by the interplay between gene and environment, which ultimately modulates the rates of molecular and cellular involution during aging. Clearly, individual humans are subject to genetic risks for age-related diseases, such as AD, cancer, diabetes, heart disease, and stroke. Other mammals share subsets of these age-related diseases, but we do not know causes of mortality in flies or worms (*2*). Because the incidence of diverse diseases accelerates exponentially with increasing age, it is difficult to critically resolve whether general age-related changes, such as the loss of skin elasticity and the slowing of reflexes, are mediated by the mechanisms that govern specific age-related diseases.

The Heritability of Life-Spans Is Small

A convergence of new and old data shows that the heritability of life-span accounts for ≤35% of its variance in short-lived invertebrates [the nematode (*3*) and fruit fly (*4*)] and in mammals [the mouse (*5*) and human (*6*, *7*)] (Table 1). Two studies of human twins attribute most (>65%) of the variance to nonshared (individually unique) environmental factors (*6*, *7*). Twins reared apart share even less heritability of life-span (*7*). We do not yet fully comprehend the nature or penetrance of environmental influences acquired during postnatal and prenatal phases or even earlier in the life of the prezygotic oocyte (*8*).

Nonheritable variations in life-span are also found in laboratory populations of inbred lines of nematodes, fruit flies, and mice. Within each inbred line, individuals show wide variations in life-span that, expressed as the coefficient of variation, approximate those of outbred populations (Table 1). Moreover, inbred worms and flies, but also outbred human populations, display multiphasic changes in mortality rates during aging, such that mortality rates initially accelerate exponentially with advancing age (Gompertzian mortality) but then decelerate markedly and even decrease among the last survivors (*1*, *2*, *9*). However, it remains possible that residual genetic variations contribute to this demographic (actuarial) heterogeneity in inbred laboratory animals (*10*).

Nonetheless, we do not depreciate the importance of genetics to the evolution of life-spans, which is exemplified by the efficacy of artificial selection for longer or shorter life-span in outbred fruit flies (*2*, *11*, *12*). Life-span is considered by evolutionary biologists to be a statistical outcome of selections for the reproductive schedule (*1*, *11*–*16*). Depending on the selection regime operating on a given population, the heritability of life-spans is like other quantitative life history parameters that show heritabilities ranging from negligible to nearly complete (*11*, *13*). It is recognized from the effects of diet restriction on life-spans of mice of different genotypes (*2*) that gene-environment interactions can greatly modify life-spans. Thus, transgenic approaches will be useful in identifying the dependency of life-span on genetic influences in different host backgrounds. It is conceivable that transgenic experiments could also assess whether genes or alleles that influence life-span within a given species may also modify the life-spans of other species. However, it seems unlikely that a few genes determine the 25-fold difference in life-spans between rodents and humans (*2*, *11*, *15*).

Table 1. Heritability and variance characteristics of life-spans in selected vertebrates and invertebrates. ND, not determined.

Species	Heritability of life-span* (%)	Coefficient of variation of life-span† (%)	Mean life-span (temp.)
Nematode (*3*)			15 days (25°C)
Within line	0 (self-fertilizing)	34	
Between lines	34	19 (16–24)	
Flies			
Fruit fly, inbred lines (*4*)			40 days (25°C)
Within line	<1		
Between lines	6–9	11	
Medfly, outbred (*9*)	ND	45	21 days (25°C)
Mouse, inbred lines (*5*)			27 months
Within line	<1	24 (19–71)	
Between lines	29	16	
Human twins (*6*, *7*)	23–35	MZ, 19; DZ, 25	72 years

*A linear model partitioned the heritability of life-spans into additive, dominant, and epistatic components (*3*–*7*). For animal models, values are "narrow sense heritability" that represents the additive component (*63*). For human twin MZ and DZ pairs from Denmark (*6*) and Sweden (*7*), environmental terms were included in the model (*63*); the values show the range of heritability across both studies. Danish twins (*6*) showed the best fit with a model of dominant heritability and nonshared environment (23 to 26%, broad sense heritability; Swedish twins, narrow sense, 35% heritable, 65% nonshared environment). †The coefficient of variation for life-span is the standard deviation of life-span in the population as a percentage of the mean life-span (*64*). Numbers in parentheses are the range of values. Variations of life-span within inbred lines could represent the microenvironment (*65*) but also residual genetic variations (*10*, *3*).

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Gene Expression in Aging

Mutations dramatically modify the life-span of fruit flies (*11*, *15*, *17–19*) and nematodes (*15*, *20–24*) through mechanisms that may be shared by common effects on metabolism and gene expression. In fruit flies, enhancer-trap systems (*25*) detect transcriptional changes of exquisite specificity in their location and timing; for example, the decreased expression of *wingless* (*wg*) is restricted to specific cells of the antennae (*23*). However, the relatively greater expression of the gene encoding heat shock protein 70 (*hsp70*) in flight muscle of old flies during stress responses is due to posttranscriptional age changes (*17*). In rodent brain and other tissues, selective changes in gene activity have also been observed (*2*), such as the increased expression of the astrocyte cytoskeletal glial fibrillary acidic protein (GFAP), which is due to increased transcription (*26*).

Experimental manipulations of life-span in flies and rodents also cause corresponding changes in gene activity. During temperature-induced shifts in fruit fly life-spans, the age schedule for decreased expression of *wg* and *engrailed* (*en*) in the adult antenna (*19*) and for increased expression of *hsp70* in muscle (*17*) is also shifted in proportion to life-span over a threefold range (Fig. 1). Accelerated age changes in gene expression occur in very short-lived mutants carrying *drd*, Hk^1, or Sh^5 (*19*) and in catalase-null flies (*17*). These cell-specific age changes could not be detected in homogenates of whole flies, which are often used for biochemical studies of aging. Taken together, the anatomic and temporal specificity of changes during aging and their scheduling in proportion to variations of life-span in different situations suggest the hypothesis that changes in gene activity during aging in flies are physiologically coordinated through humoral or neural factors. Although no data are available on how aging alters hormones or metabolites in the hemolymph of fruit flies, in certain castes of honeybees, there are increases of juvenile hormone that trigger senescence (*2*, *27*). In view of the age changes in regulatory pathways involving *en* (transcription factor) and *wg* (secreted molecule mediating intercellular signaling), it will be of interest to examine expression of these and related genes in flies of different life-spans that were selected for early and late reproduction (*11*, *12*).

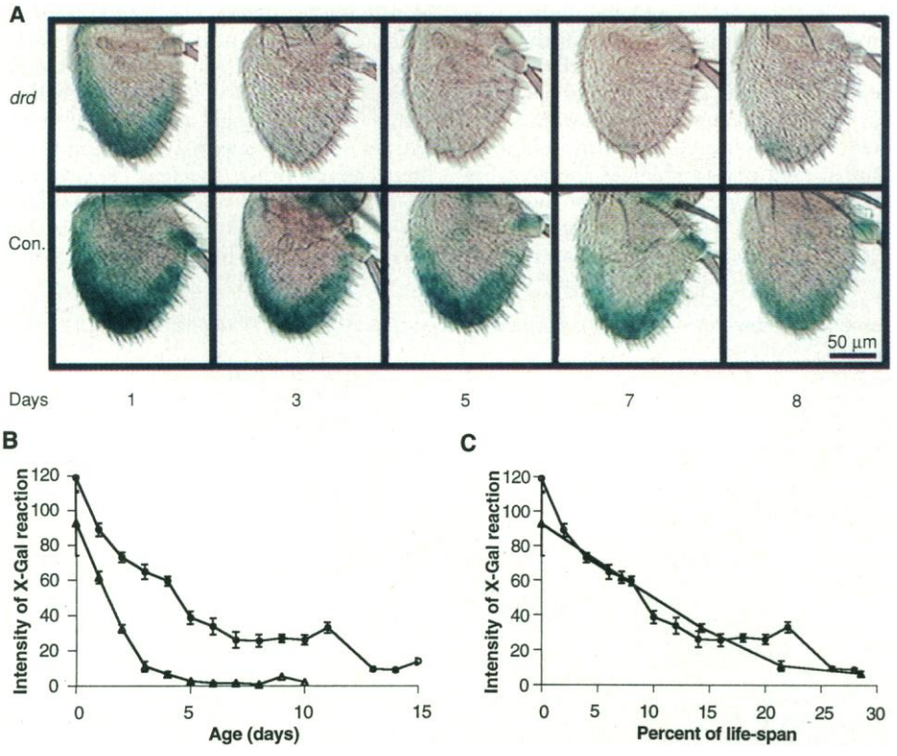

Fig. 1. Expression of the *wg* gene in fruit flies during aging changes in proportion to the life-span. (**A**) The green color shows the reporter signal from an enhancer-trap line in control (Con.) flies (life-span, 40 days) and in the short-lived mutant *drd* (life-span, 6 days). (**B**) Expression of *wg* decreases gradually during aging in control (●) antennae and more rapidly in *drd* antennae (▲). (**C**) Expression of *wg* as a percentage of life-span. Symbols are as in (B). [Figures provided by S. Helfand (*19*)] (Copyright 1997 National Academy of Sciences, U.S.A.)

The similar effects of very different mutations (*drd*, Hk^1, Sh^5) on accelerating age changes in gene expression recall the shared outcomes of defects in various genes that cause AD, all of which increase production of the amyloid-β peptide (Aβ) and lead to similar neurodegenerative changes at later ages. The potential influence of physiological factors in rat brain aging is demonstrated by the impact of food restriction, which slows the age-related increases in GFAP transcription and other markers of glial activation (*26*), while also increasing life-span (*2*, *18*).

Gene expression is also altered during aging in bakers' yeast (*Saccharomyces cerevisiae*), in which solitary mother cells sustain a finite number of asexual replicative cycles that, through budding, yield a limited number of progeny (*28–31*). Postreplicative yeast mother cells become enlarged, have changed optical properties (granularity), and may lyse during the next hours to days. Mutants selected for stress resistance (cold and nitrogen starvation) show increased budding cycle life-spans on some genetic backgrounds, for example, the *SIR4-42* allele of the *UTH2/SIR4* gene, which increases life-span and stress resistance. The *SIR* complex (silent information regulator) transcriptionally silences genes at telomeres, as well as genes required for sexual mating (*HML* and *HMR*). The mutant Sir4-42 protein causes a redistribution of Sir proteins from telomeres to the nucleolus, as also occurs in senescent wild-type yeast cells (*29*, *30*). Underexpression or overexpression of wild-type *UT4* correspondingly increases or decreases the number of budding cycles. Mutation of the *SGS1* gene, which encodes a DNA helicase with homology to the human gene for Werner progeria, also causes premature aging with redistribution of Sir3 to the nucleolus (*30*). The redistribution of telomeric silencing proteins is consistent with selective transcription of previously silenced genes, *HMRa1* (*29*) and certain subtelomeric genes, such as *URA3* (*28*). Other nontelomeric yeast genes also show altered expression during aging, for example, decreased expression of the "longevity determining genes" *LAG1* and *RAS1* (*28*). The concentration of ribosomal RNA is also lower in old yeast cells (*28*), possibly as a consequence of the redistribution of Sir proteins to the nucleolus. In certain mammalian brain neurons, the nucleolus shrinks at later ages through unknown mechanisms (*32*). In the filamentous fungus *Podospora anserina*, a long-lived mutant was mapped to a locus encoding *grisea*, a copper-activated transcription factor implicated in the mitochondrial DNA instability that occurs during senescence in this species (*31*). Taken

together, these findings suggest that selective changes of gene regulation have important roles in cell phenotypes of aging, as is widely found in development. However, it remains to be determined how many changes in gene activity during aging are secondary to other underlying causes, such as oxidative damage to molecules in the extracellular matrix as observed in mammals (*2*, *15*, *18*).

Budding cycle senescence in single yeast cells differs from the well-studied clonal (replicative) senescence of human diploid fibroblasts (*33*, *34*), in which telomeres shorten during clonal senescence in vitro and in vivo (*33*). In yeast, telomeres do not shorten during budding cycle senescence (*28*), whereas induced telomere shortening appears to increase life-span (*29*). A broad similarity, however, is selectivity of changes in transcription; so far, no examples of changes in homologous genes have come to light. In view of the increased resistance of mammalian fibroblasts to apoptosis during potentially prolonged postreplicative phases (*33*, *34*), it will be of interest to more closely examine details of cell involution and eventual lysis in postreplicative yeast mother cells.

Toward a Genetics of Longevity

Schächter *et al.* (*35*) have proposed a three-part classification of candidate loci for longevity: (i) genes with homologs that influence longevity in other species, (ii) genes that mediate cellular maintenance and repair, and (iii) genes that are associated with susceptibility to major age-related diseases.

A search is under way to find genes that are associated with longevity in humans and other mammals, with a focus on the very elderly. In centenarians, the strongest candidate is the ε*2* allele of the apolipoprotein E (apoE) gene. The frequency of the ε*4* allele, which promotes vascular disease, was 50% of that in younger controls, whereas the frequency of ε*2*, which is strongly associated with hyperlipidemia when homozygous, was higher in centenarians (*36*). Nonetheless, occasional centenarians with ε*4*/ε*4* are not demented (*37*). In Italian centenarians, the frequency of apoB with low tandem repeats (*apoB-VNTR*) is 50% of that in young controls, but this difference was not found in French and Finnish centenarians (*38*). The multigene major histocompatibility system (HLA in humans and MHC in mice) continues to spark interest as a source of longevity-enhancing alleles. Mice carrying the $H\text{-}2^d$ allele have longer life-spans, increased immune vigor, and fewer lymphomas during aging (*2*, *5*). Although centenarians show significant enrichment of up to twofold in certain alleles of the *HLA-A*,*-C*, and *-DR* series (*39*, *40*), no finding has yet been generalized across human populations.

Candidate longevity genes for humans are being identified by searches for single gene mutations that extend the life-span of the nematode *Caenorhabditis elegans*. Six induced mutations that extend life expectancy by 40 to 100% (*20*–*23*) share increased resistance to stressors, including temperature, free radicals, and ultraviolet (UV) light. The first such mutation identified was *age-1*, which doubles maximum life-span (*20*). Other nematode mutations also associate extended adult life-span with stress resistance. The greatest increases in life-span are associated with two genes that cause constitutive formation of the *dauer* larval stage (Table 1): *age-1*, which is identified with a phosphatidylinositol 3-kinase (*22*), and *daf-2*, which is identified with an insulin receptor–like gene (*23*). DAF-2 activation by the dauer pheromone is hypothesized to be mediated by PIP-3 (*23*). This mechanism would be consistent with genetic evidence that *daf-2* and *age-1* participate in an epistatic pathway (*21*) and with the greater lipid accumulation by *daf-2* mutants (*23*). The regulation of nematode life-span by insulinlike signaling is consistent with the extension of life-span in rodents by food restriction (*2*, *18*). Another set of long-lived mutants are those involving the clock gene (*clk*), which have slowed development, lengthened cell cycles, and modified adult behavior (*24*). *clk-1* encodes a short protein, an 82–amino acid tandem repeat that is highly conserved in eukaryotes; its yeast homolog *CAT5*/*COQ7* indirectly regulates the transcription of genes that modulate energy metabolism to permit growth on nonfermentable carbon sources. The longest lived *C. elegans* are *daf-2*/*clk-1* double mutants with a fivefold increase in life-span (*24*). The increase of total life-span by the dauer mutations *daf-2* and *daf-23* represents a twofold increase in the adult phase in addition to extended development.

A longevity locus for cellular maintenance is indicated by loss of function in the recently identified gene responsible for Werner syndrome, a rare autosomal recessive adult-onset progeroid with early manifestations of aging such as hair loss, skin atrophy, premature heart disease, and various tumors. The Werner gene resembles the DNA (RecQ) helicases (*41*). Loss-of-function mutations in this gene lead to impaired DNA replication or DNA repair, resulting in the accumulation of various somatic DNA mutations and rapid decrease in telomere length (*15*). In contrast to the fruit fly mutations that accelerate multiple changes in gene expression, the Werner progeria mutations do not uniformly accelerate aging; for example, there is no evidence for cognitive decline or AD. Nonetheless, because mutation of a yeast homolog also induced a progeroid phenotype (*30*), it is possible that helicase functions could mediate a wider range of cellular aging changes than previously thought. A common polymorphism in the Werner progeria gene has recently been associated with 2.7-fold higher risks of heart attacks (*41*), but the cellular mechanisms involved have not been defined.

The third category includes genes involved in age-related neurodegenerative, cardiovascular, and immunological disorders and cancer. Alzheimer's disease is an increasingly common neurological disorder of the elderly, which accounts for 70% of all cases of late-onset dementia (after 60 years of age) and currently causes greater than 100,000 deaths per year in the United States (*42*). Because the incidence of AD doubles every 5 years after 60 years of age (*42*), the incidence of AD is expected to increase further as more people survive to advanced ages. Characteristic neuropathological features of AD include neurofibrillary tangles (NFTs) and extracellular deposits of Aβ in senile plaques and cerebral blood vessels. NFTs and Aβ also accumulate to a much lesser extent in individuals who reached advanced ages without clinical dementia (*42*). Although everyone might develop AD if they lived long enough, environmental risk factors most likely interact with genetic risk factors to determine the age of onset. This argument can be extended to cancers, because carcinogenic determinants that vary with advancing age (greater than 30 years) appear to be distinct from those that are environmentally determined (*43*). The former may involve impaired DNA surveillance or activation of quiescent cells with damaged DNA. Meanwhile, impaired cell death (apoptosis), in combination with increased cellular proliferation, may underlie age-dependent decreases in the suppression of tumor formation caused by altered tissue microenvironment (*44*). For example, the accumulation of replicatively senescent fibroblasts in vivo during aging could alter the cellular microenvironment by the increased secretion of proteases and other matrix-degrading enzymes (*33*).

Genetics of AD and Cell Death

In contrast to the findings on life-spans, strong genetic effects are found in late-onset cognitive declines. In twins, the concordance with diagnosed AD (up to death) was two to threefold greater for monozygous (MZ) than for dizygous (DZ) pairs (*45*). However, the onset of AD varied widely,

with only 50% of concordant MZ or DZ pairs becoming demented within 5 years of each other (within-pair differences in onset ranged from 0 to 16 years). The number of AD cases that are attributed to known and undefined genetic risk factors decreases at later ages. This trend parallels vascular disease risk factors in twins and diminishing genetic influences on blood lipids at later ages (*46*).

Although most AD occurs in populations older than 60 years, about 5% arises before 60 years of age (*47*), when it is frequently clustered in families [early-onset familial AD (FAD)]; FAD is autosomal dominant and virtually 100% penetrant (*42*). This genetically heterogeneous condition involves defects in at least three different genes that cause indistinguishable neuropathology. The major component of brain amyloid in AD brains is a 4-kD peptide (Aβ) derived during the processing of the amyloid-β protein precursor (APP) (*42*). Several missense FAD mutations in the APP gene cluster around the Aβ domain and increase the production of Aβ. Transgenic mice with APP mutations accumulate Aβ in the brain, but without neuronal loss or NFTs (*42*, *48*). This result suggests that Aβ deposits may be necessary but are not sufficient to yield AD-like neuropathology, at least in the mouse brain. Ongoing studies may show whether other AD components such as human forms of the tau protein, a main component of NFT, or human forms of genes expressed in glia are required to induce AD in mice. In transgenic mice overexpressing wild-type APP, early death and brain abnormalities occurred in the absence of Aβ deposits. Because early death also occurs in 20% of nontransgenic mice of this strain (FVB/N), APP overexpression may accelerate a natural, age-related brain disorder (*49*).

Mutations in APP and in the presenilins PS1 and PS2 account for roughly 50% of the occurrence of early-onset FAD (*42*). The vast majority of FAD mutations occur in PS1, each being typically restricted to a single family (*42*). Despite this genetic diversity, AD may nonetheless develop from a broadly shared pathogenic process. Most FAD mutations in APP, PS1, and PS2 increase the secretion of Aβ by favoring the production of "long" Aβ, a form of the peptide with 42 rather than 40 residues, which is more prone to aggregate and to form Aβ deposits in the brain (*42*). These data argue for a central role of $A\beta_{42}$ in amyloid deposits of AD brains. Moreover, the *APOE-ε4* allele is associated with increased Aβ load in AD brains (*42*, *50*). The *ε4* allele is associated with both late-onset AD and stroke due to Aβ deposits in cerebral blood vessels (*51*). The risk for AD conferred by *ε4* is greatest for onset between 61 and 70 years of age (*47*). Meanwhile, the *ε2* allele is associated with a decreased risk for AD, which is consistent with its association with longevity (*36*).

Although functions of the presenilins are unknown, they exhibit 50% identity to the *C. elegans* protein SEL-12, which is a facilitator of the LIN-12 Notch receptor. Moreover, the death of PS1-null mouse embryos due to defects in somite segmentation indicates that presenilins play key roles in axial skeleton development (*52*). Presenilins are also substrates for a caspase-3 family protease during apoptosis. Moreover, the PS2 N141I ($Asn^{141} \rightarrow Ile$) FAD mutation confers increased susceptibility to apoptosis and increased cleavage of the PS2 protein by caspase-3 (*53*). Caspase-3–generated presenilin fragments could, in turn, also render cells more vulnerable to apoptosis. Apoptosis in aging can either be beneficial by eliminating dysfunctional cells so that they can be replaced by proliferation (homeostasis) or detrimental by eliminating irreplaceable cells such as neurons, leading to neurodegeneration. For example, in aging rodents, D2 dopamine receptor–containing neurons are lost through apoptosis, whereas apoptosis decreases the accumulation of nonfunctional T cells during food restriction (*54*).

Apoptotic death of neurons during AD (*55*, *56*) may result from impaired energy metabolism and the enhanced generation of 4-hydroxynonenal (*56*), a key mediator of neuronal apoptosis induced by oxidative stress. Alternatively, neuronal death in AD could be due to enhanced caspase-mediated cleavage of the presenilins in association with increased vulnerability to apoptosis (*53*) or to altered interactions of presenilins with the catenin family of proteins (*57*). The catenins also interact with the adematous polyposis coli (APC) tumor suppressor, the inactivation of which can lead to increased proliferation or inhibition of apoptosis owing to transcriptional activation mediated by β-catenin (*58*). Mutations in either APC or β-catenin occur in one-third of melanomas (*59*). Thus, β-catenin may become oncogenic when mutated or upregulated by inactivation of APC. Because β-catenin can also interact with the presenilins, endoproteolysis of PS1 or PS2 may serve to regulate proliferative versus apoptotic signals mediated by catenins. The involvement of the catenins in the Wingless signaling pathway of fruit flies, which is mutually inhibitory with Notch (*60*), may explain how a nematode presenilin homolog, SEL-12, facilitates the LIN-12 Notch receptor.

Alternate Life Histories

Genetic variants in the invertebrate models described above show that altered scheduling of aging can arise from induced mutations, with great shortening or lengthening of life-spans. Moreover, environmental factors may determine alternate life histories within the same population. An instructive example is the 10-fold difference in life-spans of female worker bees (*Apis mellifica*), which have rapid senescence and life-spans of months, whereas queens of the same genotype show much slower senescence during life-spans of many years of active egg production. These alternate life histories in females are determined by exposure of larvae to nutrients and juvenile hormones.

Brown trout (*Salmo trutta*) also have several coexisting life histories, with the giant ferox trout living more than five times as long as smaller sized trout (*2*, *61*). At a critical body size, some adult brown trout switch from plankton feeding to piscivory, which allows faster growth and, contrary to predictions from food-restriction theory (*2*, *18*), a much longer life-span (*61*). A possible genetic basis is the much higher prevalence of a lactic dehydrogenase allele (*Ldh-5*) in ferox than in the small, short-lived brown trout in the same local population. In the killifish (*Fundulus heroclitus*), geographic subpopulations differ in LDH alleles and isozyme activities that were shown experimentally to alter rates of development (*62*).

When these examples are considered together with the *C. elegans* mutations that modify metabolism and life-span, it seems plausible that metabolic regulation may be a general feature of life history variants. These examples are also consistent with the evolutionary theory of life histories, in which selection for the duration and frequency of reproduction indirectly modifies the potential life-span (*11*, *13–15*). The extensive plasticity in adult life-spans is also represented in the recent major increases of human life-span, although it is not obvious how this increase could have resulted from natural selection.

Conclusions

During recent centuries, technological advances that have allowed a higher quality of both life and general health have also revealed an untapped potential of the human genome to support major increases in life expectancy at all ages (*1*). Nonetheless, the explosive increase of cancer, vascular disease, and AD at later ages was not widely experienced in historical human populations, so that there has been minimal selection against these diseases at

their present age of occurrence (*2*, *11*, *14*, *15*). Ironically, genetic tools that have been developed in the various genome projects now allow easy identification of genetic risk factors for conditions that may compromise health in later years. One might consider that, if the human life expectancy should approach the present record of 122 years, some existing gene polymorphisms that may be "lying in wait" could rise up to challenge the quest for health at advanced years. The growing inventory of genetic and environmental factors affecting the life-span, along with an understanding of gene-to-gene and gene-environment interactions, should arm us well for the continuing battle with morbidity. Genetic studies of age-related human diseases and longevity mutants of animal models have identified many risk factors that affect metabolism and resistance to stress. Future studies of animal and cell models of aging should identify many paths, some of them convergent, by which environmental factors modify genetic risk factors in aging. In summary the relatively minor heritability of human life-span at advanced ages and the variable penetrance of genetic risk factors imply that choice of life-style profoundly influences the outcomes of aging.

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63. The value for nematodes is the grand mean of calculations from three different experimental paradigms, each replicated (19, 34, and 45% heritability) (*3*).
64. The coefficient of variation is a dimensionless number, calculated as $(SD/X) \times 100$ for each species, where SD is the standard deviation for life-spans in that population and X is the mean life-span. The following species were examined: nematode *C. elegans*: Bristol hermaphrodites (mean, three experiments) and mean of Bristol, Bergerac, and F_2 (six lines) [calculated by T. E. Johnson (personal communication) from (*3*)]; fruit fly (*Drosophila melanogaster*): 25 genotypes, each identically heterozygous for chromosome 2 [calculated by M. Tater (personal communication) from (*4*)]; medfly (*Ceratitis capitata*) [calculated by J. Carey (personal communication) from (*9*)]; mouse (*Mus musculus*), 20 inbred lines [calculated by R. A. Miller (personal communication) from (*5*)]; and human twins, who were Danish born from 1870 to 1880, with genders averaged to compute grand means for MZ and DZ twin pairs (*6*).
65. Variations in life-spans must also depend on local conditions. For example, total life-spans of *C. elegans* can be more than threefold as long if a lack of nutrients during development triggers the *dauer* larval stage; the *dauer* may last 70 days without altering the adult phase, once food becomes sufficient (*2*, *20–23*). Social and reproductive interactions can also increase mortality risk in flies and mice. The present sampling of populations under protected conditions nonetheless has similar variations in life-span that give a sense of baseline variations [see also (*10*, *25*)].

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