

Proposal Article

A Proposal to Sequence Genomes of Unique Interest for Research on Aging

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THE recent sequencing of genomes, including the human genome, has revolutionized biomedical research. The projected genome sequencing of a large number of mammalian species, such as several primates, will offer extraordinary opportunities for studying genome evolution and to better understand the structure and dynamics of the human genome. Most target organisms for sequencing were chosen because of their usefulness as biomedical models or because of their phylogeny in relation to the human genome to address comparative and evolutionary issues (<http://www.genome.gov/10002154>). The biology of longevity, however, has been neglected in these considerations. Yet one of the most striking and mysterious differences among mammals is the wide variability in longevity (1). Understanding the differences in aging rates among species is a major biological puzzle. Herein we argue that studying genome evolution across species with different life spans has the potential to change our understanding of aging processes. Thus, longevity should also be taken into consideration when selecting target organisms for sequencing. As a first step, we propose the sequencing of three organisms of unique interest for aging research: the naked mole-rat (*Heterocephalus glaber*) whose record longevity of 28.3 years makes it the longest-lived rodent (2), the white-faced capuchin monkey (*Cebus capucinus*) which can live > 50 years (3), and the bowhead whale (*Balaena mysticetus*), the longest-lived mammal with estimates suggesting that it may live > 200 years (4).

Recent research has elucidated several gene systems that can regulate aging and multiple age-related diseases in short-lived model organisms (<http://genomics.senescence.info/genes/models.html>). Nonetheless, the longevity effects of these genes are modest relative to the lengthening and shortening of life spans during evolution. Mammals display at least a 40-fold variation in maximum longevity (1,5). We still do not know why different species of similar body plan, biochemistry, and physiology can age at such different rates, but these differences must be seated in the genome (6).

In the same way it is possible to analyze sequence data from species with different brain sizes to obtain candidate

genes (7), we think it is now computationally possible to analyze genome sequence data from species with different life spans for candidate genes that can be experimentally tested. Computational strategies to understand the genetic basis of differences in aging between humans and closely-related species would define a new paradigm for gerontological research. For example, nearly all vertebrates share the amyloid- β peptide sequence associated with Alzheimer's disease in humans, yet the accumulation of Alzheimer-like changes varies widely among species (8). What other gene differences, one may ask, modulate the effect of the amyloid gene during aging? Mammals also show major species differences in cancer type and incidence, which may be traced to specific gene differences. As humans, and one of the longest-lived animal species, it is in our keen interest to study the genetic features that contribute to the evolution of longevity and that determine our susceptibility to age-related diseases.

Mammalian model systems have been typically chosen to study specific human diseases, with an emphasis on short-lived genotypes that show early-onset conditions. This is especially true for rodent models such as mice and rats that live up to 4–5 years (5). It seems timely for us to consider very long-lived models, such as the naked mole-rat. Naked mole-rats commonly live into their 20s, which is in stark contrast to similar-sized rodent species such as mice (1,2). We propose that sequencing the naked mole-rat genome will provide not only another model of human disease but primarily the first model of resistance to chronic diseases of aging.

Several studies have identified gene candidates in the evolution of human traits including longevity (7,8). Although the chimpanzee genome is likely to yield many interesting candidates, it seems urgent to us to sequence the genome from at least one additional long-lived primate lineage. Capuchin monkeys are, after humans and great apes, the best example of a long-lived primate lineage with specimens reported to live > 50 years in captivity. This is much longer than other New World monkeys (such as marmosets) that typically do not live more than two decades and whose genome is currently being sequenced, and is

remarkable considering that capuchin monkeys are much smaller than great apes (3).

Longevity of some whale species likely exceeds the human life span. Plausible evidence from bowhead whales indicates longevity of > 200 years (4). Although studying in vivo aging in bowhead whales has obvious difficulties and limitations, we believe that we can obtain from its genome sequence useful clues for identifying the genetic and molecular mechanisms that allow some whales to live longer than humans.

Certainly, these three organisms may not provide a complete understanding of how evolution extends life span. Nonetheless, having the genome sequence of the proposed organisms will allow us to start prodding the mechanisms behind the evolution of longevity in mammals, and in primates in particular. Identifying even a fraction of the genomic features determining longevity and disease susceptibility in primates would be a major breakthrough. With the current rapid progress in sequencing technologies, we expect that other species of interest for research on aging will be targeted for sequencing in the future.

Conclusion

The proposed genomic resources will provide researchers powerful new tools for studying the evolution of longevity and for establishing the naked mole-rat as a unique long-lived model for biomedical research. These resources will help guide experiments in more traditional models with potentially many implications for understanding human aging and age-related diseases. Finally, considering longevity as a factor in selecting organisms for genome sequencing will allow researchers to start studying the genetic factors that allow some species to be more resistant than humans to certain diseases.

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The full proposal is available online (<http://genomics.senescence.info/sequencing/>).

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