COMMENTARY

Genomic evidence for the evolution of human postmenopausal longevity

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Rates of Aging Evolve

In PNAS, Flavio Schwarz et al., in the laboratories of Ajit Varki and Pascal Gagneux at the University of California, San Diego/Salk Institute Center for Academic Research and Training in Anthropogeny (CARTA), report an apparent genetic signature of past selection for persistent cognitive competence at postfertile ages in humans (1). This can seem surprising because evolutionary explanations for aging (senescence) and its varying rates across species begin with the declining force of natural selection across adulthood (2). Within this framework, the rate at which selection weakens—and so the resulting rate of decline in performance with age—depends upon adult mortality risk. The higher the likelihood of surviving to older ages, the greater the fitness benefit for allocation to somatic maintenance and repair (3). Of special importance here, the strength of selection against senescence also depends on the fitness gains possible at older ages, as illustrated by slower physiological decline with age in indeterminant growers, like fish that continue to increase in rate of egg production with ever-increasing size (2).

Human Riddles

With these general theoretical tools for explaining why aging rates vary, the case of humans initially seems quite puzzling. Women's fertility ends at about the same age that fertility ends in other female hominids, the great apes. However, although our closest living relatives grow decrepit and rarely live into their 40s (4) [even in captivity (5)], women can remain healthy and productive well past menopause (6). Longer adult lifespans that include a distinctive postmenopausal stage (7, 8) stand out as derived in our lineage. How could selection have favored this pattern of slower human aging?

Schwarz et al. (1) investigated the phylogenetic history of alleles of the immunoregulatory receptor *CD33* and their effects on late-age Alzheimer's dementia (LOAD). Using recently sequenced genomes of other hominids, they found that the *CD33* allele, which is protective against LOAD, is derived in humans. If protection against LOAD is the main phenotypic effect of the allele, it would only have been favored if there were fitness benefits from cognitive competence at older ages.

Due to Ancestral Grandmothering?

As Schwarz et al. (1) surmise, the apparent puzzle is resolved by the grandmother hypothesis, which proposes that human postmenopausal longevity evolved when subsidies from ancestral grandmothers allowed mothers to have next babies before their previous offspring could feed themselves. Because longer-lived grandmothers could help more, they passed greater longevity to more grandsons and granddaughters, increasing longevity in subsequent generations (9–12).

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Schwarz et al. (1) measured expression levels of *CD33* in humans and chimpanzees, finding the expression of one splice form (CD33M) in humans to be fourfold higher than in chimpanzees. Such increased expression, they hypothesize, would have accompanied brain expansion, raising the risk of LOAD in ancestors whose longevity had increased with grandmothering. That risk would have favored the protective allele through fitness benefits gained only at older ages. The same scenario could account for polymorphisms of the *APOE* gene, which encodes for the plasma protein APOE, where the allele that is derived in humans is also protective against the late-life onset of Alzheimer's disease (13, 14). Schwarz et al. also suggest that as expanded capacities to transmit information evolved with human language, competent elders of both sexes became especially valuable to both kin and community (1).

Of special importance for Schwarz et al.'s interpretation of the genomics (1), both *CD33* and

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APOE remain polymorphic in all human populations despite the protection afforded by the derived alleles. The authors link this aspect to the declining force of selection with age. When protective alleles gave inclusive fitness benefits only in postfertile individuals, polymorphisms would persist because the derived alleles were not advantageous to young adults. Surveying an array of other genes linked to cognitive decline, Schwarz et al. (1) again found both polymorphic haplotypes and derived alleles that are protective, the pattern expected if expanding brains increased the risks of late-age cognitive decline in ancestral populations with the derived longevity of genus *Homo* maintained by grandmother effects.

How Old Is Human Longevity?

The fossil and archaeological records continue to be crucial lines of evidence about what happened and when in human evolution. Those "hard" lines of evidence—stone tools with cut-marked bones of large animals and increased cranial capacity in genus *Homo*—have long made meat eating and brain size favored candidates to explain the evolution of our longevity (14). Schwarz et al.'s demonstration (1) shows that genomics offers a line of evidence into the character and timing of life history shifts that might themselves have been the crucial foundation for many distinctively human features (15, 16). Although the authors found the derived *CD33* allele only in modern humans, the small number of Neanderthal and Denisovan genomes currently available cannot rule out similar polymorphisms in those taxa. Schwarz et al. (1) note that both the global distribution and apparent absence of recent selection in the *CD33*, *APOE*, and other derived protective alleles indicate they evolved before modern humans emerged in Africa. How long before might eventually be revealed by statistical methods yet to be developed (1).

The claim that distinctive human longevity and our characteristic postmenopausal life stage are very ancient will meet skepticism from some, based on the firm evidence that human life expectancies at birth only rose above 50 y in the 20th century. However, it is not a lack of old people that accounts for average lifespans of 40 y or less through most of human experience. That misleading average, and its change with the demographic transition, is strongly affected by the number of brief lives of dying babies and children.

The grandmother hypothesis is consistent with Sarah Hrdy's continuing demonstrations of the central importance of cooperative breeding in our lineage, including effects on infant development and social cognition (17–19). However, in the grandmother hypothesis an ancestral shift away from the independent mothering of the great apes occurred when drying and more seasonal environments reduced the availability of foods that just-weaned juveniles could handle. Then the few older females still surviving as their fertility declined could increase their fitness in a novel way; and those novel benefits at older ages resulted in selection for increased somatic maintenance and repair. In simulations of Peter Kim's two-sex agent-based model of the grandmothering scenario (11, 12), even very weak grandmothering drives populations from an ancestral ape-like equilibrium to a human-like one. At the ancestral equilibrium fewer than 1% of the adult females are past their fertility, but their helpful grandmothering drives populations to a new equilibrium with about 40% of the adult females past their fertility, very like the age structures of modern hunter-gatherers.

Those simulations assume mutations in unidentified "longevity genes." Comparisons between humans and chimpanzees have provided hints about some of the physiological mechanisms involved (20, 21). But with growing sophistication about the complex genomics, Schwarz et al. (1) show that even more direct comparisons between humans and chimpanzees can reward researchers who know where to look.

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