The different paths to 100[1–4]

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ABSTRACT

Many people believe that the older a person gets, the sicker he or she becomes. The result can be quite a pessimistic view of very old age. If this were true, most if not all centenarians would have significant disability. However, ≈90% of centenarians in a population-based study were functionally independent at the average age of 92 y. Thus, to achieve extreme old age, a much more enabling point of view emerges: the older an individual gets, the healthier he or she has been. Centenarians thus have the potential to represent a model of relative resistance to age-related diseases and slower aging. Currently, 1 in every 10 000 persons in the United States is 100 y of age or older. This prevalence is quickly changing, however, and it is likely that most industrialized nations will soon experience twice that prevalence, or one centenarian per 5000 persons. The ability to survive to extreme old age appears to be the result of a complex combination of genetics, environment, lifestyle, and luck. Understanding the genetics of the very old, and identifying the molecular drivers of longevity (or of mortality), is a potentially powerful approach to discovering and targeting the pathways mediating aging and disease susceptibility and developing preventive and therapeutic agents that will allow more of the population to age in good health.   *Am J Clin Nutr* 2006;83(suppl):484S–7S.

KEY WORDS   Centenarians, longevity, dementia, Alzheimer disease, compression of morbidity, genetics, *APOE* ε-4

INTRODUCTION

One in ten thousand (0.01%) persons in the United States is 100 y of age or older (1). Many assume that, because of the prevalent misconception that "the older a person gets, the sicker that person gets," centenarians are the most unhealthy and debilitated among the elderly. Given that the prevalence of Alzheimer disease (AD) is ≈50% for persons aged ≥85 y, one could assume that if the prevalence continues to increase at even older ages, most of the oldest old should have AD (2, 3). One population-based study did in fact report a dementia prevalence of 100% among a sample of centenarians (4). However, population-based centenarian studies from Denmark, Sweden, Germany, and the United States have reported dementia-free rates of ≈30% (5, 6). In the New England Centenarian Study, 12% of centenarians were living independently (7). Among centenarians who did show cognitive impairment, >90% were cognitively intact until well into their 90s (8). For some reason, a notable portion of centenarians escape dementia altogether; of those who don't, clinical demonstration of dementia is delayed in many until very late in life.

The hypothesis of compression of morbidity, as proposed by Fries in 1980 (9), seems to be valid among the very long-lived with respect to functional impairment. Onset and accumulation of disease-related disability can be compressed into the last years of life for many centenarians; however, it is also possible to live to 100 y and older with a long history of age-related disease. Researchers have speculated that some special adaptive ability, or functional reserve, allows some to survive to very old age despite the presence of diseases that would otherwise be associated with significant mortality risk and disability at much younger ages (10–14).

Evert et al (15) looked at the timing of age-related disease in a retrospective cohort study of >400 centenarians. Prevalence and age of onset of heart disease, hypertension, diabetes, skin cancer, nonskin cancer, osteoporosis, stroke, Parkinson disease, thyroid conditions, and chronic obstructive pulmonary disease were surveyed. On the basis of the results, the subjects were divided into 3 distinct groups: survivors, delayers, and escapers. Forty-two percent were classified as survivors, persons who had been diagnosed with at least one age-related disease before the age of 80 y; 45% were delayers, in whom no age-associated disease had been diagnosed until after the age of 80 y; and 13% fell into the category of escapers, persons who reached centenarian status without a previous diagnosis of any of the 10 diseases of aging studied.

Because most centenarians remain functionally independent through their early 90s, these results appear to support the presence of an adaptive mechanism or functional reserve. Subset analysis of the data for the most deadly of the age-related diseases (ie, heart disease, nonskin cancer, and stroke), however, showed that persons either delay or escape these; few centenarians were survivors of such diseases.

These results suggest several routes to longevity may be possible. The survivor, delayer, and escaper profiles represent different centenarian phenotypes and probably also reflect different underlying genotypic and environmental interactions. It also appears that most centenarians have a history of delaying or escaping cognitive impairment, because in the very old, cognitive impairment is perhaps the most reliable marker of impending

mortality (16, 17). Such delay or escape could be due to cognitive reserve in the face of an underlying progressive neuropathologic process or could be due to the absence of such a process. Neuropsychological–neuropathologic correlation studies are critical to determining which of these scenarios leads to delayed cognitive impairment.

NEUROPSYCHOLOGICAL-NEUROPATHOLOGIC CORRELATIONS

Supporting the observation that 12–25% of centenarians appear not to have clinical dementia, a subset of these persons also appear to have no dementia according to neuropathologic examination (18–21). In a case series of 14 centenarians consenting to undergo both neuropsychological and postmortem neuropathologic assessments, 4 subjects had clinical dementia rating (CDR) (22) scores of zero (indicating no impairment). These subjects without dementia also did not meet Braak and Braak neuropathologic criteria for AD (23) and did not have neuritic plaques on examination (24, 25). Six subjects with CDR scores > 0.5 (very mild to severe dementia) had neuropathologic evidence of AD. The remaining 4, who had CDR scores ≤ 0.5, had neuropathology consistent with probable AD and yet did not clinically demonstrate the disease premortem. Snowden (26) observed a 102-y-old who on examination did not meet the clinical criteria for dementia yet was discovered on autopsy to have significant AD pathology. Such cases where there is discordance between the clinical and pathologic examinations suggest that some persons have a functional reserve that allows for minimal or no cognitive impairment in the presence of significant pathology.

Dementia incidence among the oldest old

One meta-analysis of 9 epidemiologic studies found the rate of increase in dementia prevalence declined among octogenarians and appeared to plateau at ≈40% at age 95 y (27). In a longitudinal study of older persons living in Cache County, UT, the incidence of both dementia and AD increased almost exponentially until ages 85 to 90 y but declined after 93 y for men and 97 y for women (28). Another meta-analysis of dementia incidence studies noted a significant age effect in which the increase in incidence rates slowed at advanced ages and women were consistently at higher risk of developing AD than were men (29).

Causes of dementia

Of interest are observations that the frequencies of various causes of dementias differ between centenarians and younger cohorts. Researchers in the Danish Centenarian Study reported that 50% of the dementia cases among centenarians were due to pure vascular disease (5). An autopsy series of 13 Japanese centenarians with at most mild cognitive impairment showed vascular but not AD pathology (19). It is likely that rare causes of dementia become more common among centenarians because persons who are prone to develop AD die at younger ages, leaving survivors to develop other neurodegenerative illnesses, such as vascular dementia, Pick disease, and Lewy Body disease (24). This selecting out of a survivor cohort that is less likely to develop potentially lethal age-related diseases is known as demographic selection (30).

Why would Alzheimer disease slow or plateau?

A genetic example of demographic selection is the decreased frequency of the apolipoprotein E (APOE) ε-4 allotype in the oldest old. Persons who are homozygous for APOE ε-4 have a 2.3–8.0 times greater risk of developing AD than does the general white population (31). The allelic frequency of APOE ε-4 falls off in the oldest age groups, which is likely because of its association with AD and vascular disease (32). Interestingly, the effect of APOE allotype on AD incidence appears to decrease with age at these very old ages (33), presumably because those who survive have other genetic variations or lifestyle factors that protect them from the deleterious effects of their APOE allotype.

THE GENETICS OF EXTREME AGE

It has been suggested that persons who reach extreme old age have genetic variations that affect the basic mechanisms of aging and result in decreased susceptibility to age-associated diseases (34). Persons who achieve oldest age likely lack many of the disease gene variations that substantially increase risk of premature death (35). More controversial are the possible existence of longevity-enabling genes that might actually protect persons from basic causes of aging or age-related illnesses (36).

The progressive selection for genetically fit persons at very old age provides the basis for a simpler model of aging and longevity. Centenarians might be rare because a complex set of environmental and genetic variables coexist to allow such survival. Studies of centenarian pedigrees suggest that family members are more likely to share such sets of variables than the general population. One study analyzed the pedigrees of 444 centenarian families in the United States that included 2092 siblings of centenarians (37). Compared with the US 1900 birth cohort, male siblings of centenarians were 17 times as likely, and female siblings were 8 times as likely, to reach 100 y of age. Such elevated relative survival probability values support the possibility that family members can share genetic and environmental factors that are important to survival to extreme old age (38, 39).

LONGEVITY GENES?

Discovery of genetic variations that explain even a small percentage of variations in relative survival probability will provide important clues to the cellular and biochemical mechanisms that mediate aging and susceptibility to age-associated diseases. Until recently, only one genetic variation had been reproducibly associated with exceptional longevity (although the degree of this association varies according to ethnicity). Schachter et al (32) observed that the frequency of the APOE ε4 allele decreases with advancing age. One of its counterparts, the APOE ε2 allele, becomes more frequent with advancing age in whites (40).

The elevated relative survival probability values found among the siblings of centenarians support the utility of studies to determine which genetic region or regions, and ultimately which genetic variations, centenarians and their siblings have in common that confer their survival advantage (38). Centenarians and their siblings from the New England Centenarian Study were used in a genome-wide sibling pair study of 308 persons belonging to 137 families with exceptional longevity. Using nonparametric analysis, significant evidence for linkage was noted for a locus on chromosome 4 at D4S1564 with a maximum logarithm-of-odds score of 3.65 ($P = 0.044$) (41). A detailed haplotype map was created of the chromosome 4 locus that extended over 12 million base pairs and involved the genotyping of >2000 single-nucleotide polymorphism markers in 700 centenarians and 700

controls. The resulting genetic association study identified a haplotype marker within the microsomal transfer protein (*MTP*) gene as a modifier of human life span (42). All known single-nucleotide polymorphisms for *MTP* and its promoter were genotyped in 200 centenarians and 200 young controls. After haplotype reconstruction of the area was completed, a single haplotype, which was underrepresented in the long-lived persons, accounted for most of the statistical distortion at the locus ($\approx$15% among the subjects compared with 23% in the controls). Because MTP is rate-limiting in lipoprotein synthesis, it might affect longevity by subtly modulating this pathway. Considering that cardiovascular disease is significantly delayed among the offspring of centenarians and that 88% of centenarians either delay or escape cardiovascular disease and stroke beyond the age of 80 y, it follows that the frequency of genetic polymorphisms that play a role in the risk of such diseases would be differentiated between centenarians and the general population (15, 43).

A study of Ashkenazi Jewish centenarians and their families identified another cardiovascular disease pathway and gene that is differentiated between centenarians and controls (44). Researchers noted that HDL and LDL particles were significantly larger among the centenarians and their offspring, and that particle size also differentiated between subjects with and without cardiovascular disease, hypertension, and metabolic syndrome. In a candidate-gene approach, the researchers then searched the literature for genes that affect HDL and LDL particle size; genes encoding hepatic lipase and cholesteryl ester transfer protein emerged as candidates. Comparing centenarians and their offspring with controls, levels of one variant of cholesteryl ester transfer protein (the 405 valine allele) were noted to be significantly greater among those with or predisposed to exceptional longevity.

CONCLUSIONS

Discovering genes that promote longevity while compressing morbidity and disability toward the end of life will provide possible explanations to how the aging process mediates susceptibility to age-related diseases and how this susceptibility might be modulated. Human "longevity genes" are likely to influence aging at its most basic levels and to affect a wide range of genetic and cellular pathways simultaneously. Mapping of the centenarian genome will be critical; comparing single-nucleotide polymorphism frequencies implicated in disease in centenarians with frequencies in persons with disease will identify clinically relevant polymorphisms. The ultimate objective, of course, is that these gene discoveries will lead to the identification of therapeutic targets and the development of therapeutic agents to enable more of the population to age as centenarians do. ✣

REFERENCES

1. Perls TT, Bochen K, Freeman M, Alpert L, Silver MH. Validity of reported age and centenarian prevalence in New England. Age Aging 1999;28:193–7.
2. Hebert LE, Scherr PA, Beckett LA, et al. Age-specific incidence of Alzheimer's disease in a community population. JAMA 1995;273:1354–9.
3. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA 1989;262:2551–6.
4. Blansjaar BA, Thomassen R, Van Schaick HW. Prevalence of dementia in centenarians. Int J Geriatr Psychiatry 2000;15:219–25.
5. Andersen-Ranberg K, Vasegaard L, Jeune B. Dementia is not inevitable: a population-based study of Danish centenarians. J Gerontol B Psychol Sci Soc Sci 2001;56:P152–9.
6. Hagberg B, Bauer Alfredson B, Poon LW, Homma A. Cognitive functioning in centenarians: a coordinated analysis of results from three countries. J Gerontol B Psychol Sci Soc Sci 2001;56:P141–51.
7. Silver MH, Jilinskaia E, Perls TT. Cognitive functional status of age-confirmed centenarians in a population-based study. J Gerontol B Psychol Sci Soc Sci 2001;56:P134–40.
8. Hitt R, Young-Xu Y, Silver M, Perls T. Centenarians: the older you get, the healthier you have been. Lancet 1999;354:652(letter).
9. Fries JF. Aging, natural death, and the compression of morbidity. N Engl J Med 1980;303:130–5.
10. Wilson R, Barnes L, Bennett D. Assessment of lifetime participation in cognitively stimulating activities. J Clin Exp Neuropsychol 2003;25:634–42.
11. Scarmeas N, Stern Y. Cognitive reserve and lifestyle. J Clin Exp Neuropsychol 2003;25:625–33.
12. Richards M, Sacker A. Lifetime antecedents of cognitive reserve. J Clin Exp Neuropsychol 2003;25:614–24.
13. Lee JH. Genetic evidence for cognitive reserve: variations in memory and related cognitive functions. J Clin Exp Neuropsychol 2003;25:594–613.
14. Stern Y. The concept of cognitive reserve: a catalyst for research. J Clin Exp Neuropsychol 2003;25:589–93.
15. Evert J, Lawler E, Bogan H, Perls T. Morbidity profiles of centenarians: survivors, delayers, and escapers. J Gerontol A Biol Sci Med Sci 2003;58:232–7.
16. Hassing LB, Johansson B, Berg S, et al. Terminal decline and markers of cerebro- and cardiovascular disease: findings from a longitudinal study of the oldest old. J Gerontol B Psychol Sci Soc Sci 2002;57:P268–76.
17. Nybo H, Petersen HC, Gaist D, et al. Predictors of mortality in 2,249 nonagenarians–the Danish 1905-Cohort Survey. J Am Geriatr Soc 2003;51:1365–73.
18. Silver M, Newell K, Hyman B, Growdon J, Hedley-Whyte ET, Perls T. Unraveling the mystery of cognitive changes in old age: correlation of neuropsychological evaluation with neuropathological findings in the extreme old. Int Psychogeriatr 1998;10:25–41.
19. Itoh Y, Yamada M, Suematsu N, Matsushita M, Otomo E. An immunohistochemical study of centenarian brains: a comparison. J Neurol Sci 1998;157:73–81.
20. Samuelsson SM, Alfredson BB, Hagberg B, et al. The Swedish Centenarian Study: a multidisciplinary study of five consecutive cohorts at the age of 100. Int J Aging Hum Dev 1997;45:223–53.
21. Mizutani T, Shimada H. Neuropathological background of twenty-seven centenarian brains. J Neurol Sci 1992;108:168–77.
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4.
23. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–59.
24. Silver MH, Newell K, Brady C, Hedley-White ET, Perls TT. Distinguishing between neurodegenerative disease and disease-free aging: correlating neuropsychological evaluations and neuropathological studies in centenarians. Psychosom Med 2002;64:493–501.
25. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease Neurology 1989;39:1159–65.
26. Snowdon DA. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med 2003;139:450–4.
27. Ritchie K, Kildea D. Is senile dementia "age-related" or "ageing-related"? – evidence from meta-analysis of dementia prevalence in the oldest old. Lancet 1995;346:931–4.
28. Miech RA, Breitner JC, Zandi PP, Khachaturian AS, Anthony JC, Mayer L. Incidence of AD may decline in the early 90s for men, later for women: the Cache County study. Neurology 2002;58:209–18.
29. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry 1998;55:809–15.
30. Carey JR, Liedo P, Orozco D, Vaupel JW. Slowing of mortality rates at older ages in large medfly cohorts. Science 1992;258:457–61.

31. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.

32. Schachter F, Faure-Delanef L, Guenot F, et al. Genetic associations with human longevity at the APOE and ACE loci. Nat Genet 1994;6:29–32.

33. Breitner JC, Wyse BW, Anthony JC, et al. APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. Neurology 1999;53:321–31.

34. Cutler RG. Evolution of human longevity and the genetic complexity governing aging rate. Proc Natl Acad Sci U S A 1975;72:4664–8.

35. Schachter F. Causes, effects, and constraints in the genetics of human longevity. Am J Hum Genet 1998;62:1008–14.

36. Perls T, Kunkel LM, Puca AA. The genetics of exceptional human longevity. J Am Geriatr Soc 2002;50:359–68.

37. Perls TT, Wilmoth J, Levenson R, et al. Life-long sustained mortality advantage of siblings of centenarians. Proc Natl Acad Sci U S A 2002; 99:8442–7.

38. McCarthy MI, Kruglyak L, Lander ES. Sib-pair collection strategies for complex diseases. Genet Epidemiol 1998;15:317–40.

39. Olofsson P, Schwalb O, Chakraborty R, Kimmel M. An application of a general branching process in the study of the genetics of aging. J Theor Biol 2001;213:547–57.

40. Rebeck GW, Cheung BS, Growdon WB, et al. Lack of independent associations of apolipoprotein E promoter and intron 1 polymorphisms with Alzheimer's disease. Neurosci Lett 1999;272:155–8.

41. Puca AA, Daly MJ, Brewster SJ, et al. A genome-wide scan for linkage to human exceptional longevity identifies a locus on chromosome 4. Proc Natl Acad Sci U S A 2001;98:10505–8.

42. Geesaman BJ, Benson E, Brewster SJ, et al. Haplotype-based identification of a microsomal transfer protein marker associated with the human lifespan. Proc Natl Acad Sci U S A 2003;100:14115–20.

43. Terry DF, Wilcox M, McCormick MA, Lawler E, Perls TT. Cardiovascular advantages among the offspring of centenarians. J Gerontol A Biol Sci Med Sci 2003;58:M425–31.

44. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. JAMA 2003;290: 2030–40.