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Genetics of exceptional longevity

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Abstract

Centenarians exist at the extreme of life expectancy and are rare. A number of pedigree and molecular genetic studies indicate that a significant component of exceptional longevity is genetically influenced. Furthermore, the recent discovery of a genetic locus on chromosome 4 indicates the powerful potential of studying centenarians for genetic factors that significantly modulate aging and susceptibility to age-related diseases. These studies include siblings and children of centenarians. Siblings have a significantly increased propensity to achieve exceptional old age and have half the mortality risk of their birth cohort from young adulthood through extreme old age. The children of centenarians are emerging as a promising model for the genetic and phenotypic study of aging relatively slowly and the delay and perhaps escape of important age-related diseases.

Keywords: Centenarian; Oldest old; Longevity; Genetics; Heritability; Clustering; Demography

1. Nature versus nurture

When addressing the genetic role in aging, most reviews to date have cited the Scandinavian twin studies. These studies calculated the heritability of life expectancy to be 20–30% (Ljungquist et al., 1998). In other words, environmental differences accounted for 70–80% of the variability in age at death for these sets of twins. The other message inherent in these results is that the genetic effect is too weak and much too complex to expect the ability to decipher specific genetic variations that have substantial effects upon the basic biology of aging and/or the susceptibility to age-associated diseases. However, the oldest twins in these studies were in their mid to late 80s and therefore address perhaps the ability to achieve average life expectancy (or a bit older) but not the ability to achieve extreme old age.

The Scandinavian studies make sense in the context of average humans, who in modern societies have an average life expectancy of about 79 years. If average humans are born with an average set of genetic polymorphisms, it will be differences in their habits and their environments that will explain the variability in their life expectancies. Supporting this notion is a study of Seventh Day Adventists indicating that optimal health related behaviors adds an additional 8 years of average life expectancy (Fraser and Shavlik, 2001). It was recently revealed that 75% of Americans are overweight and a third are obese. Far too many people still use tobacco and far too few regularly exercise. Thus, it is no wonder that our average life expectancy is about 10 years less (along with many more years of disability) than what our average set of genetic variations is capable of achieving for us. On the other hand, if one consistently maintains healthy habits, for example remaining lean, regular strength training, not smoking, a diet conducive to lean body mass and cardiovascular health, then on average, one should expect to live to their mid-eighties. Furthermore, the compression of morbidity hypothesis would predict that the majority of those years would be spent in good health (Vita et al., 1998).

2. Familial clustering

The extent to which genes dictate the ability to live 15–20 years beyond what the average set of genetic variations are capable of achieving is not clear, though thus far, studies of centenarians and their families imply a distinguishing role. In gathering pairs of siblings as part of our New England Centenarian Study, we identified 3 families that clearly demonstrate segregation for extreme old age (Perls et al., 2000). In addition, another family was identified in a publication by the New Hampshire Antiquarian Society that gave a historical account of centenarians living in that state from 1705 to 1877. We set out to expand these pedigrees

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and to determine if the clustering could be attributed to chance or if genetics must be playing a causative role. The pedigrees demonstrating vertical transmission of extreme longevity are shown in Fig. 1. Omitted family members died at age 18 years or younger, or died at an age less than 90 years because of trauma. The illustrated gender of certain members was altered for anonymity. Ages were validated using vital records and US Federal census entries.

Family A is composed of one male and four females aged 100 or older in one generation living in the 17th and 18th centuries. In family B, the individuals of note were born in the 19th and 20th centuries and seven are centenarians. In

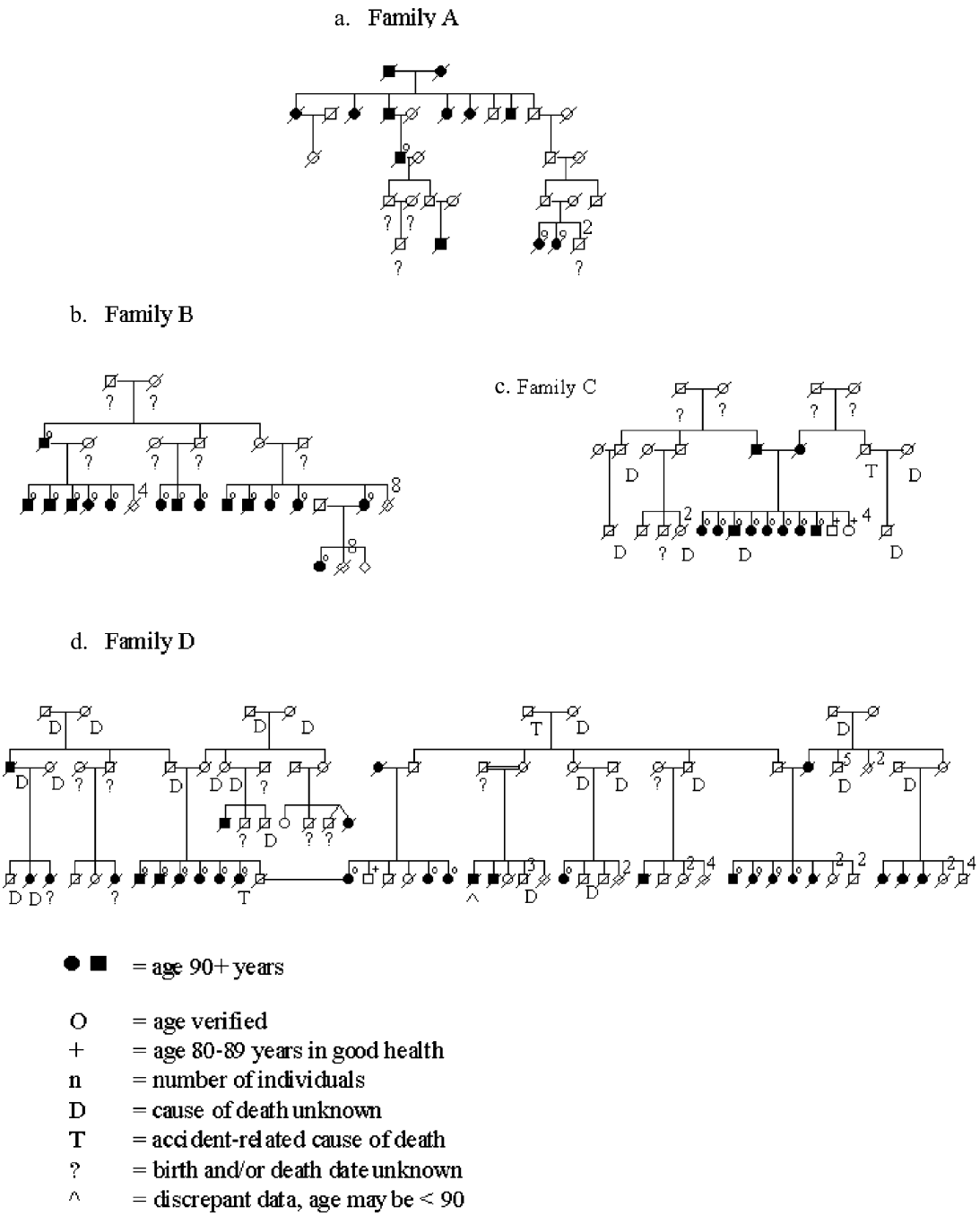

Fig. 1. Four families demonstrating vertical transmission of extreme longevity. Omitted family members died at age 18 years or younger, or died at an age less than 90 years because of accidental trauma. The illustrated gender of certain members was altered for anonymity. Ages were validated using vital records and US Federal census entries. (a) Family A is composed of 1 male and 4 females aged 100 or older in one generation living in the 17th and 18th centuries. (b) In Family B, the individuals of note were born in the 19th or early 20th century and 7 are centenarians. (c) In family C, there is a sibship of 13 children with 8 reaching extreme old age (range: 90–102 years old). (d) In family D, there are two branches linked together by a marriage in the 3rd generation. These different branches orginate from the same small region in Norway. In the 3rd generation, 23 of 46 individuals achieved extreme old age (range 90–106 years old).

family C, there is a sibship of 13 children with 8 reaching extreme old age (range: 90–102 years old). In family D, there are two branches linked together by a marriage in the 3rd generation. In the 3rd generation, 23 of 46 individuals achieved extreme old age (range: 90–106 years old).

Cohort life tables for the years 1900, 1850 and 1801 were used to estimate the probability of individuals in Fig. 1 surviving to their specified ages. For earlier birth cohorts, such as those encountered in the family A pedigree, the 1801 cohort life table was used as a conservative estimate of probability. These specific probabilities were then used to calculate a binomial probability of obtaining N individuals achieving their specified ages from a random sample of M individuals belonging to specific birth cohorts. Probabilities were calculated for the single most impressive generation of each family. Probabilities would be even lower if the individuals achieving extreme old age from other generations were also taken into account.

The random chance of encountering the six siblings age 90 and older in family A is one in 10^9. In family B, there are three sibships that compose all grandchildren of two individuals. The chance of 13 of the 20 grandchildren living past 90 is about one in 10^{18}. In one of the three sibships, 5 of 16 siblings achieved age 100 or older, also an extremely rare observation if left to chance. In the case of family C, the chance of 8 siblings reaching at least 90 years is less than one in 10^{13}. Dominant inheritance is a possibility in this pedigree, given that both parents are affected and the children are largely or entirely affected. Though pedigree D appears to represent three unrelated branches, these branches originate from the same small region of Norway and therefore there may be a common ancestor. Nonetheless, treating the branches separately, the chance of encountering the 9 of 14 grandchildren reaching at least age 90 in the left branch is one in 10^{12}. The middle branch's grandparents had 12 of 38 grandchildren live to at least age 90, a chance occurrence of one in 10^{11}. The right branch's grandparents had 8 of 26 also living to at least age 90; a chance observation of one in 10^8.

One could argue that these small probability values could be increased by a factor of ten (personal correspondence, Anatoli Yashin) taking into account the similar environments siblings were raised in that would have played a role in increasing their childhood probability of survival (for example, better living conditions). Even taking into consideration such a correction factor, the above probability values remain smaller than 1 per the number-of-families-in-the-world today, so clearly there is familial aggregation that cannot be explained by random chance.

The above probability values are smaller than 1 per the number-of-families-in-the-world today, so clearly there is familial aggregation that cannot be explained by random chance alone. Several points argue in favor of shared genetic factors rather than environmental factors affecting such a survival advantage. Namely, two of the four families include cousins achieving extreme old age and these relatives are unlikely to have a common childhood environment. Also, the four described families come from distinct backgrounds. While this implies genetic as well as environmental diversity, one cannot imagine any environmental components shared by these families that would be responsible for extreme longevity. One would not necessarily expect that the families have the same genetic cause, but only that genetics plays an important role.

3. Siblings

To further explore the genetic aspects of exceptional old age, we analyzed 444 centenarian pedigrees containing 2092 siblings (Perls et al., 2002). Sibling death rates and survival probabilities were compared to US national levels using the Social Security Administration's life table for the cohort born in 1900. The death rates of the siblings of centenarians relative to the 1900 birth cohort are shown in Fig. 2, revealing a lifelong sustained reduction of mortality risk by approximately one half even up through very old age.

Effects of some environmental and behavioral factors that siblings could have in common early in life may remain strong throughout life. It would make sense that some of these are primarily responsible for the shared survival advantage at young to middle age. Some of these effects might not become evident until older age. However, in general, environmental characteristics of siblings such as socio-economic status, life styles and region of residence are likely to diverge as they grow older. Thus if the survival advantage of the siblings of centenarians is mainly due to environmental factors, the advantage should decline with age. Therefore, the stability of relative risk over the wide age range would suggest that the advantage is attributable more to genetic than environmental factors.

Whereas death rates reflect the current intensity of death at a moment in time, a survival probability reflects the cumulative experience of death up to that moment in a cohort's life history. Thus, a relatively constant advantage from moment to moment (as seen in the relative death rates) is translated into an increasing survival advantage over a lifetime (relative survival probabilities). As revealed in Table 1, the relative survival probabilities (RSP) for male and female siblings of centenarians begin to markedly rise at about age 60, ultimately reaching 17 and 8.2, respectively, for achieving age 100 compared to the general experience of their 1900 birth cohorts.

The marked increase in RSP and sustained mortality advantage at extreme ages could be consistent with the forces of demographic selection in which genes and/or environment that predispose to longevity win out over those that are associated with premature or average mortality. The substantially higher RSP values for men at older ages perhaps reflect the much higher mortality risk men experience at these ages and thus the increased relative

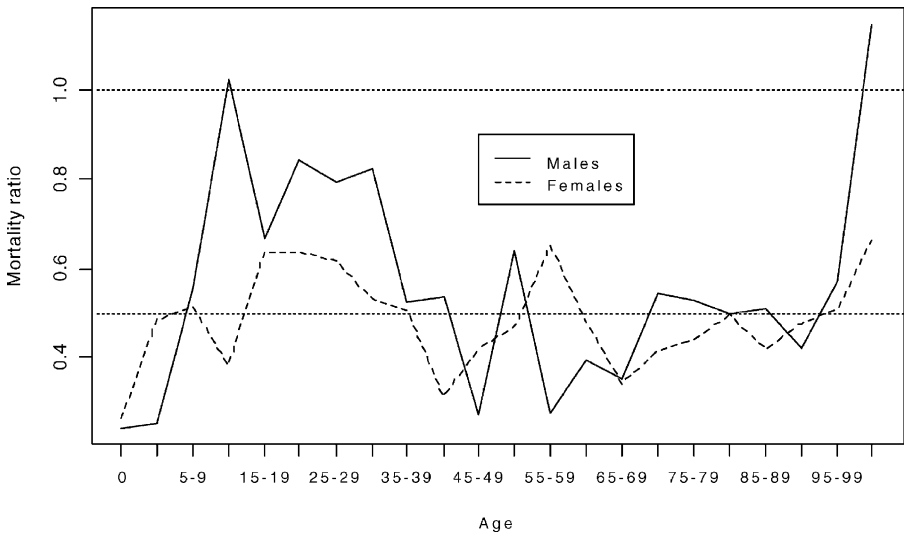

Fig. 2. Relative death rates by sex: siblings of centenarians versus the US 1900 cohort provided by the Social Security Administration (6). The dashed lines at 1.0 and 0.5 as represent equal mortality and half the mortality rate of the 1900 birth cohort at large.

benefit they experience from genetic variations conducive to extreme survival (Perls and Fretts, 1998).

Despite the fact that males generally make up only 15% of centenarians they tend to be better off than their female counterparts both in terms of physical and cognitive function. This would at first seem paradoxical since women seem so much better able to achieve extreme old age. One explanation may be that compared to women, men have to be in particularly good condition to achieve extreme old age. Those who are not, die before reaching the centenarian mark. These observations may represent a demographic crossover in which women are better off than men at younger old age, but then men, though much fewer in number, become better off at extreme old age.

4. Future phenotypic and genetic discoveries: pitfalls and opportunities

Though we observed that functional impairment was compressed towards the end of life among centenarians, anecdotally we noted that a number of these individuals had long histories of an age-related disease. Perhaps an unusual adaptive capacity or functional reserve allowed some of these individuals to live a long time with what normally would be regarded as a debilitating if not lethal disease while delaying its attendant morbidity and mortality by as much as decades. To explore this hypothesis amongst our centenarian sample we conducted a retrospective cohort study exploring the timing of age-related illnesses (Evert

Table 1
Relative survival probabilities with 95% confidence intervals (CI) of siblings of centenarians versus US 1900 cohort

Age	Males			Females		
	Relative survival probability	Lower 95% CI	Upper 95% CI	Relative survival probability	Lower 95% CI	Upper 95% CI
20	1.00	1.00	1.00	1.00	1.00	1.00
25	1.00	0.99	1.01	1.01	1.00	1.02
30	1.01	1.00	1.02	1.02	1.01	1.03
35	1.01	1.00	1.03	1.03	1.01	1.04
40	1.03	1.01	1.05	1.04	1.02	1.06
45	1.04	1.02	1.06	1.06	1.04	1.07
50	1.08	1.05	1.10	1.08	1.06	1.09
55	1.10	1.07	1.13	1.10	1.08	1.12
60	1.18	1.15	1.21	1.12	1.09	1.14
65	1.29	1.25	1.33	1.16	1.13	1.19
70	1.48	1.42	1.53	1.24	1.21	1.28
75	1.68	1.60	1.77	1.36	1.31	1.41
80	2.03	1.90	2.16	1.54	1.47	1.60
85	2.69	2.47	2.91	1.83	1.73	1.93
90	4.08	3.62	4.54	2.56	2.39	2.74
95	8.35	6.98	9.71	4.15	3.73	4.57
100	16.95	10.84	23.07	8.22	6.55	9.90

et al., 2003). Three morbidity profiles emerged from the analysis of health history data. Survivors, who were diagnosed with an age-associated disease before the age of 80 were 42%. In the sample 45% were Delayers, subjects who were diagnosed with age-associated disease at or after the age of 80, beyond the average life expectancy for their birth cohort. The third morbidity profile, the Escapers, who made up 13% of the centenarian sample, attained their 100th birthday without the diagnosis of the 10 common age-associated diseases investigated. The Survivor, Delayer and Escaper routes represent different centenarian phenotypes and thus likely different genotypes as well. The categorization of centenarians into these and other groups (e.g. cognitively intact, smokers, etc.) should prove to be useful in the study of factors that determine exceptional longevity.

Though the centenarians may be a scientifically valuable cohort for the discovery of genetic correlates of exceptional longevity, phenotypic measures might be correlates of marked frailty rather than of the ability to achieve extreme old age. As suggested by two recent studies, the children of centenarians, however, appear to be unusually healthy and may well prove to be worthwhile to study for both phenotypic and genetic determinants of the ability to live to 100 years and older. Terry and colleagues studied the health histories of 177 unrelated children of centenarians compared to birth cohort matched controls. The controls were the children of parents born in the same years as the centenarians but at least one of whom died at average life expectancy. After multivariate adjusted analyses, the centenarian offspring had reduced relative prevalences of 56% for heart disease, 66% for hypertension, and 59% for diabetes (Terry et al., 2003). Thus, the offspring of centenarians demonstrate a markedly reduced prevalence of diseases associated with aging, in particular for cardiovascular disease and cardiovascular risk factors.

Barzilai and colleagues studied the lipid profiles among Ashkenazi Jewish centenarians, their children and the children's spouses (the controls in the study). Both the male and female children had significantly higher high density lipoprotein-cholesterol (HDL-C) levels compared with controls and the males also had significantly lower LDL-cholesterol (LDL-C) levels. These two studies support the hypothesis that phenotypic and therefore likely genotypic characteristics conducive to exceptional longevity are transmitted in long lived families and, furthermore, factors related to cardiovascular health seem to play a particularly important role (Barzilai et al., 2001).

5. Genes predisposing for exceptional longevity

Discovering genetic variations that explain even 5–10% of the variability in survival to extreme old age could yield important clues about the cellular and biochemical mechanisms that impact upon basic mechanisms of aging and susceptibility to age-associated diseases. Until recently, only one genetic variation has been replicated to demonstrate an association with exceptional longevity, but even that finding might vary according to ethnicity and other unknown sources of stratification. Schachter and colleagues noted the frequency of the apolipoprotein E ε-4 allele to decrease markedly with advancing age (Schachter et al., 1994). One of its counterparts, the ε-2 allele, becomes more frequent with advanced age among Caucasians. Presumably the drop out at earlier age of the ε-4 allele is because of its association with 'premature' mortality secondary to Alzheimer's disease and heart disease. The fact that just one genetic variation has emerged has made some scientists quite pessimistic that others will be found.

However, the elevated RSP values found among the siblings of centenarians, nonetheless, supported the utility of performing genetic studies to determine what genetic region(s) and ultimately what genetic variations centenarians and their siblings have in common to confer such a survival advantage (McCarthy et al., 1998). Centenarian sibships from the New England Centenarian Study were used in a genome wide sibling pair study of 308 individuals belonging to 137 families demonstrating exceptional longevity. Using non-parametric analysis, significant evidence for linkage was noted for a locus on chromosome 4. These linkage results indicated the significant likelihood that there exists a gene or genes that exert a substantial positive influence upon the ability to achieve exceptional old age (Puca et al., 2001). The next step will be to replicate this result with an independent set of families and to proceed with a single nucleotide polymorphism analysis of the locus to find the gene(s) playing a significant role in the marked survival advantage of these individuals.

Pursuing a long, involved as well as expensive sibling pair study begs the question of what the utility of finding a gene and polymorphism common to centenarians would be. Rather than fitting the myth of the older you get the sicker you get, centenarians typically achieve their age by living 90% of their very long lives independently (Hitt et al., 1999). Discovering genes that could impart such an advantage should help in the understanding of how the aging process increases susceptibility to diseases associated with aging and how this susceptibility might be modulated.

Individuals who achieve extreme old age likely lack many of the variations (so called 'disease genes') that significantly increase the risk of premature death by predisposing to various lethal diseases, age- and non-age-associated. More controversially, there might also exist genetic variations that confer protection against basic mechanisms of aging and/or age-related illnesses (so called 'longevity enabling genes'). Comparison of single nucleotide polymorphism frequencies of genes implicated in disease between centenarians and individuals with the diseases should reveal clinically relevant polymorphisms. Another approach that researchers are in the early stages of understanding is differential gene expression in models known to slow the aging process such as caloric restriction

(Lee et al., 1999). Such applications may prove to be another potent filter for discovering longevity enabling genes. The hope of course is that these gene discoveries will lead to the identification of drug targets—drugs that would allow people to become more centenarian-like by maximizing the period of their lives spent in good health.

6. Conclusions

The heterogeneity of how people age represents a broad spectrum of the relative importance of environmental, genetic and stochastic determinants of survival (Martin, 2002). The extremes of that spectrum, either people who age prematurely, for example those with a progeroid syndrome, or those who live to extreme old age, for example centenarians, may be able to tell us something about relatively rare factors that allow those individuals to fall into these extreme categories. Richard Cutler, in what is now a classic paper in Gerontology, proposed that relative few genetic changes were necessary to uniformly decrease the aging rate of many different physiological functions (Cutler, 1975). The progressive selecting out of more and more genetically fit individuals with very old age, termed demographic selection, lays the foundation for a simpler model for sorting out the genetics of aging and longevity. Those at the extremes of the 'how well we age' spectrum may have certain genetic characteristics that incombination are highly advantageous but also rare in the population at large. If so, these differences might have little impact on the total variation in human life span, even if their effect is quite significant for the relatively few individuals involved. Alternatively, these longevity-associated alleles could be more common than previously thought since their existence could be masked by infant mortality (which was high at the turn of the last century) and poor health habits that cause premature mortality.

The careful phenotyping of numerous animal and human models of aging and the collection of genetic material along with the current explosion in molecular genetics data and techniques are likely to soon fill important gaps in the aging puzzle. In the meantime, while we experience this very exciting time in aging research, it is important to keep in mind that most people already have the ability to achieve significantly older age in better health. Patients should realize that when it comes to aging well, the anti-aging industry's free lunch of eternal youth is nothing but hucksterism. On the other hand, taking the significant effort to change one's health related habits for the better, such as strength training, becoming lean, smoking cessation and stress reduction could translate into a gold mine of healthy years in the future. In other words, much of our ability to live into at least our early to mid-eighties in good health is determined by our long term behavior. To add another 20 years beyond age 85, however, probably requires a genetic advantage. Such an advantage will hopefully be much better understood in the near future.

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