Guest Editorial

Discovering the Secrets of Successful Longevity

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Harry is a 102-year-old artist who has been recruited into several studies designed to evaluate the phenotype and genotype of his longevity (1). It could be suggested that Harry happened to impose restrictions on his lifestyle, the benefits of which are only being realized today. Or maybe, Harry is just “lucky” to have made it to the tail end of survival. However, Harry and others with exceptional longevity seem to be showing us that neither of these scenarios is responsible for living to extreme old age.

First, when asked about his lifestyle, Harry admits to a lack of any exercise or physical activity. He has been overweight for parts of his life, he did not adhere to any restrictive diets, and he smoked most of his life. Overall, he does not have a lifestyle that in any way could be considered conducive to longevity. In fact, relatively few centenarians have reported an interaction with the environment that would suggest a possible impact on longevity.

On the other hand, Harry’s father (born in 1872) lived to over the age of 90, much beyond the life expectancy of his birth cohort, suggesting the presence of inheritance, not luck, in the longevity of this family. While age of death does not usually show a strong correlation between parents and their children, this is not the case in subjects with exceptional longevity. These subjects are born to families that are 5 to 18 times more likely to have members reaching extreme old age (2,3), suggesting that genetics is an important factor when studying this population. Moreover, such “risk” associated with longevity, and its mode of inheritance in these families, supports the notion that there are only a few genes that modulate this phenotype. Indeed, a study of siblings of centenarians provided encouraging evidence of longevity loci, and efforts to find and characterize specific genes is underway (4).

But, how are these genes responsible for Harry’s longevity? Perhaps his longevity is the result of the absence of numerous genes or alleles that are associated with age-related morbidity and mortality, rather than a gene (or very few genes) that actively prevent age-related diseases. If indeed these alleles affect life span, their frequency may decrease with very old age, reflecting poor survivor odds for the subjects who carry these alleles. The study of Korean centenarians by Choi et al. (5) is shedding more light on the unique genetic aspects of centenarians. Contrary to previous studies of Caucasian cohorts (6), the study demonstrates that the frequencies of two important polymorphic alleles, an angiotensinogen-converting enzyme (ACE) and apolipoprotein-E (gene) (APOE-4), in centenarians are similar to those seen in the younger population. This particular ACE polymorphism is associated with increased incidence of cardiovascular disease such as coronary heart disease, left ventricular hypertrophy, and type 2 diabetes mellitus, while subjects with APOE-4 are at an increased risk for developing Alzheimer’s dementia and coronary heart disease, both largely related to this altered lipid profile. Because these alleles present risks for diseases leading to mortality, their frequency is expected to decrease with age. Indeed, while the frequency of these alleles did decrease with age in several populations, noted by the author, they did not change much with age in the Korean population. Yet, the fact that the frequency of these important alleles is similar in centenarians suggests that Korean centenarians are protected “downstream” from these alleles.

Harry, our 102-year-old man, does not have the ACE allele but he does carry the APOE-4 allele. Despite its presence, however, Harry scored 30 out of a possible 30 on the Mini-Mental State Examination, taken when he was 100. Korean centenarians are less protected from cognitive decline if they carry the specific APOE-4 rather than any other allele. The lack of decline in frequencies of these two “risky” alleles in Korean centenarians, and Harry’s avoidance of cognitive decline or death in the presence of a “risky” allele, support the continuous search for a few genes that are conducive to increased life span, even in the presence of “bad” alleles. The development of a genetic “kit” that assesses one’s risk for age-related disease might become a specific aging prevention tool. However, the finding that some alleles are deleterious in some populations while they are neutral in others indicates the significant danger in assuming a specific outcome given certain genotypes in something as complex as aging or age-related diseases. Either large genetic epidemiological studies that sort out these cohort-dependent differences and/or functional studies that are able to link specific allotypes with pathogenic pathways, which then become the key to a diagnostic test or intervention, will be necessary for any utility to emerge from these types of observations.

The promising prospects of learning the secrets of longevity from people exhibiting such a trait underscore the need for uncovering their clinical characteristics, as exemplified in correlating alleles to cognitive function. In a second paper in this issue, Evert et al. (7) demonstrate some unique aspects of another population of centenarians. While approximately 15% of these centenarians had strokes, the median age of onset of this event was approximately 91 years
in male and female centenarians. Similarly, while approximately 40% had some form of heart disease, the median age of diagnosis was approximately 90 years in male and female centenarians. Indeed, for most of the diseases incurred by centenarians, the median age of diagnosis was around 90 years of age. Thus, while the majority of centenarians are free of any of these diseases, those with these diseases had an average onset several decades after the average life expectancy for their birth cohort.

Up until a recent hospitalization for suspected influenza, Harry had never received life-saving medical intervention (i.e., without which he might not have survived). However, some centenarians have had pacemakers, various other operations, and treatment for cancers, which could have contributed to their longevity. In order to account for this variability, Evert et al. suggested classifying centenarians by three criteria. The most interesting for our biological quest may be the “escapers” (32% of male and 15% of female centenarians). These subjects had reached their 100th birthday without encountering any of the common age-related diseases. The second subclass is the “delayers”—the onset of age-related disease is delayed until at least the age of 80 (approximately 40% of male and female centenarians). Finally, there are the “survivors”—their onset of age-related disease is prior to age 80 (24% of male and 43% of female centenarians). This subgrouping is based on the distribution of reported age of onset of age-related diseases. The retrospective nature of this study makes some degree of reporter bias likely but the findings are consistent with the decreased year-to-year mortality risk noted for this cohort by the same research group (3). It is possible that such subgrouping may be associated with the biological markers of longevity. For example, some of the “survivors” and “delayers” may have a decrease in the frequency of many “risky” alleles, while “escapers” may have proactive longevity genes, overcoming the potential risks of many “risky” alleles. And of course there are a myriad of other possible combinations of environmental exposures and protective and risky alleles. The importance of this clinical subgrouping may become apparent with further exploration of biological characteristics.

It is important to realize that centenarians are at the relative end of their lives. We have performed hundreds of tests on the plasma and serum of centenarians and could not identify any important characteristic associated with protection from disease. However, it is quite possible that what kept the centenarians in good health was a factor that was significantly better when they were much younger. We reasoned that if longevity was inherited, we would identify such factors in their offspring. Indeed, such research has been fruitful, and plasma high-density lipoprotein (HDL) cholesterol level has been shown to be dramatically increased in approximately 40% of the offspring of centenarians (8). Harry’s daughters have plasma HDL cholesterol levels of approximately 90, which are over two standard deviations above the mean. Furthermore, while plasma HDL was shown to decrease with age, its levels were correlated with the cognitive functioning of centenarians (9). Harry’s HDL cholesterol is 63, quite high for a man at any age, and his cognitive function is outstanding. This suggests that clinical, genetic, and biological characteristics can all be observed in families with exceptional longevity. This approach would ensure the ability to control for additional age-matched cohort, and determine if and which biological/familial factors are affecting the health of the centenarians’ offspring.

Identifying the secrets of longevity seems an interesting and fruitful area of research. It is worthwhile to take this avenue as long as we are assured, by subjects with exceptional longevity like Harry, that prevention of age-related disease is associated not only with a longer but also with a significantly better quality of life.

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REFERENCES