A long, healthy life is a desire and priority for most people. Genetic factors for longevity do not fully explain healthy aging. Recent research suggests that, in addition to other factors, healthy aging is at least in part the result of protective genetic variants for Alzheimer’s disease (AD) and coronary artery disease (CAD).

The World Health organization has reported that global life expectancy has continued to increase. Recent estimates place the life expectancy of someone born in 2015 at 71.4 years [1]. While improvements in longevity are indisputable, increased numbers of individuals suffering from aging-related diseases, including AD, CAD, and cancer, make it imperative to gain a better understanding of the factors influencing healthy aging. Healthy aging has been defined by Erikson, Bodian, et al. as disease-free aging in individuals aged 80 years or more, without medical interventions [2]. Healthy aging is a major focus for many health and government organizations as the proportion of the population over 65 years of age increases. Without effective treatments for the major age-related disorders, this increase in the aging population will place an unprecedented burden on healthcare systems and economies. In fact, disease prevention efforts have become a higher priority in public health and research [3]. Moreover, genetic studies have established several loci contributing to longevity [4]. Unfortunately, exceptional longevity does not always coincide with healthy aging. Because healthy aging represents an important goal individually and in society, a question of vital importance remains—is healthy aging a stochastic process or the result of different biological mechanisms leading to longevity?

In a recent study published in the journal Cell, Erikson, Bodian, et al. addressed this question by examining a well-characterized group of healthy elderly individuals from the Wellderly Study (appropriately named) [2]. The group comprises individuals over the age of 80 years with no presence of chronic disease or chronic use of medication. Analysis of the frequency of longevity alleles in the Wellderly subjects demonstrated no evidence of enrichment of genetic variants associated with longevity. This clearly suggested that factors independent of simple longevity influenced the probability of achieving healthy aging. To identify these factors, the authors performed whole-genome sequencing (WGS) in 511 individuals from the Wellderly study and compared them to WGS data from 689 young adults (20–44 years of age) from the Inova Translational Medicine Institute (ITMI), a pre-term birth cohort [2].

Both common and rare genetic variations were examined. The overall genetic risks for the five most common age-related disorders, AD, CAD (heart disease and stroke), cancer, and diabetes were evaluated. No associations with genetic risks for cancer or diabetes were observed. By contrast, significant decreases in common genetic risks for AD and CAD diseases were observed in the Wellderly subjects compared to controls. Interestingly, part of the reduced risk for both of these disorders was driven by a decrease in the frequency of the ε4 allele of the APOE (apolipoprotein E) gene in the Wellderly cohort. Indeed, APOE ε4 is the most common risk factor for AD and is roughly associated with a threefold increase in risk among subjects who carry one copy of APOE ε4. This allele is also associated with an increased risk for CAD, although this increase is more modest than that associated with AD. APOE is a major lipoprotein in blood and the central nervous system, and is responsible for cholesterol transport. As a result, APOE ε4 has also been associated with many lipid-metabolism traits, suggesting that good lipid profiles might be associated with healthy aging. Overall, the comparison of these two cohorts suggested that a reduced risk for aging-related diseases constituted a mechanism—at least part—for healthy aging.

Although no SNP reached genome-wide significance in common variant genome-wide association studies (GWAS) in the Wellderly subjects, three loci did provide suggestive evidence of a trend in association with healthy function of aged individuals, including a region within the major histocompatibility (MHC) locus. Indeed, SNPs within this cluster, as well as within a second locus, KCNE4 (potassium channel, voltage-gated subfamily E regulatory subunit 4), have been previously associated with cognitive phenotypes, providing further support that a significant portion of the healthy aging phenotype might be associated with healthy cognition [7]. The third locus, a region containing the sodium-dependent, low-affinity carnitine transporter gene SLC22A4 (solute carrier family 22, member 4) has been previously linked to levels of carnitine (an essential amino acid required for healthy mitochondrial function, known to decrease with age). This region demonstrated evidence of association in the Wellderly subjects.

Furthermore, to examine the role of rare variants in aging, the researchers conducted a GWAS using the SKAT-O method [optimal SNP-set (sequence) kernel association tests]. The most significant variant association was found with the COL25A1 locus (collagen type XXV, α1 subunit) in the elderly. Nine rare missense variants were observed in this gene for 10 people in the Wellderly cohort, as opposed to none in the ITMI cohort. Interestingly, this gene encodes a protein found in β-amyloid plaques in the AD brain [8]. Consequently, these findings raise the...
possibility that rare variants in COL25A1 might reduce Aβ deposition or lower the toxicity of Aβ plaques. This in turn might lead to a reduced risk for cognitive impairment, while increasing the likelihood of healthy aging. However, no risk variants in COL25A1 have been reported in AD to date.

Of note, two major limitations of the current study surface. First, although healthy aging in individuals >80 years of age represents an extreme phenotype, the sample size of 511 healthy aging individuals is relatively small when undertaking both GWAS and WGS studies. Thus, this experimental setup contains too low a statistical power to detect genome-wide significant results in both analyses. A second limitation is the lack of a replication cohort which could further validate the data. Together, these caveats limit the interpretation of these results. Although it seems clear that risk factors for AD and CAD are reduced in healthy aging (Table 1), specific genes and variants that unambiguously influence healthy aging await larger sample sizes.

Nevertheless, the idea that protective variants can provide a genetic basis for healthy aging that is distinct from longevity is an important concept that will facilitate shaping future efforts in identifying novel therapeutic targets through genetics. For instance, the PCSK9 (propprotein conver-
tase subtilisin/kexin type 9) gene embodies a well-known protective genetic risk factor for CAD. Its discovery has highlighted a novel putative therapeutic target and subsequent work is rapidly translating this information into future clinical therapies [9]. The findings reported by Eric Topol and Ali Torkamani’s laboratories suggest that protective variants similar to PCSK9 may exist for other phenotypes. The identification of these variants will be essential in contributing to the development of strategies aiming to achieve healthy aging. Indeed, we believe that scientific efforts aimed at characterizing protective factors should be a priority in AD, CAD, as well as in other diseases hindering healthy aging.

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References

Table 1. Lipid Transport, Endocytosis, and Immunity Pathways Enriched in AD and CAD GWAS Signals

<table>
<thead>
<tr>
<th>Pathway</th>
<th>AD</th>
<th>CAD</th>
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<tr>
<td>Shared pathways</td>
<td>Cholesterol transport endocytosis</td>
<td>Cholesterol transport endocytosis</td>
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<td>Immune response</td>
<td>Immune response</td>
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<td>Other pathways</td>
<td>Hemostasis</td>
<td>Protein metabolism</td>
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<td>Protein folding</td>
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<td></td>
<td>Protein ubiquitination</td>
<td>Extracellular matrix organization</td>
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<td></td>
<td>Clathrin/ADP adaptor complex</td>
<td>Hematopoietic cell lineage</td>
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*GWAS Pathway analyses in AD and CAD (compiled from [4–6]) demonstrate the overlap in enrichment for three specific pathways: lipid transport, endocytosis, and immunity. This type of analysis indicates that functional preservation of these pathways might be vital to healthy aging.