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Genes for a “Welllderly” Life

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Abstract

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 (yr) [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 80 yr or older, without medical interventions [2]. Healthy aging is a major focus for many health and government organizations as the proportion of the population over 65yr 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. Since 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 Welllderly Study (appropriately named) [2]. The group comprises individuals over the age of 80 yr with no presence of chronic disease or chronic use of medication. Analysis of the frequency of longevity alleles in the Welllderly subjects demonstrated no evidence of enrichment of genetic variants associated with longevity. This clearly suggested that factors independent of

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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 Welllderly study and compared them to WGS data from 689 young adults (20-44 yr) from the Inova Translational Medicine Institute (ITMI), a pre-term birth cohort [2].

Both common and rare genetic variations were examined. The overall genetic risk 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. In contrast, significant decreases in common genetic risks for AD and CAD diseases were observed in the Welllderly subjects compared to controls.

Interestingly, part of the reduced risk for both of these disorders was driven by a decrease in the frequency of *APOE ε4* alleles in the Welllderly cohort. Indeed, *APOE ε4* is the most common risk factor for AD and is roughly associated with a three-fold 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 which is 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 single nucleotide polymorphism (SNP) reached genome wide significance in common variant genome-wide association studies (GWAS) in the Welllderly 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, the SNPs within this cluster, as well as within a second locus, *KCNE4* (Potassium Channel, Voltage Gated Subfamily E Regulatory Beta 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 a 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 Welllderly 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, alpha 1 subunit) in the elderly. Nine rare missense variants were observed in this gene for ten people in the Welllderly 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 yr represents an extreme phenotype, the sample size of 511 healthy aging individuals is rather 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, 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 Proprotein Convertase Subtilisin/Kexin Type 9 (*PCSK9*) 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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Table 1
Lipid Transport, Endocytosis and Immunity Pathways Enriched in AD and CAD GWAS Signals

GWAS Pathway analyses in AD and CAD (compiled from references 4-6) demonstrate the overlap in enrichment for three specific pathways: lipid transport, endocytosis and immunity. This type of analysis indicates that the functional preservation of these pathways might be vital to healthy aging.

	AD	CAD	Type II Diabetes
Shared pathways	Cholesterol Transport	Cholesterol Transport	
	Endocytosis	Endocytosis	
	Immune Response	Immune Response	
	Hematopoietic cell lineage		Hematopoietic Cell Lineage
Other pathways			
	Hemostasis	Protein Metabolism	Tight Junction
	Protein Folding	Development	Adherens Junction
	Protein Ubiquitination	Extracellular matrix organization	Calcium Signalling pathway
	Clathrin/AP2 adaptor complex		Complement and Coagulation Cascades
	Hematopoietic cell lineage		PPAR Signalling Pathway
			Ether Lipid Metabolism
			TGF- β signaling pathway
			Antigen processing and presentation