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Translational Article

Special Issue on Genetics and Aging

Guest Editorial

The Genetics of Age-Related Health Outcomes

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IT has been more than a decade since the sequencing of the human genome (1,2), and the decade anniversary is approaching for development of the HapMap project (3). During this decade, we have also seen the burgeoning of genome-wide association (GWA) studies (4). This special issue of the *Journal of Gerontology Medical Science* has aimed to assess what we have learned about associations between age-related health outcomes and specific genetic markers as well as more general genetic influences on aging. Summaries and synthesis of these findings are provided by leading researchers of model organisms and human populations. The material presented by these authors may be placed in a framework, which identifies four levels of the heritable and nonheritable determinants of individual aging

1. Inherited genetic differences.
2. Exogenous somatic damage from infections, inflammogens, physical trauma, stress, and toxins.
3. Endogenous somatic damage to DNA and long-lived proteins from metabolic processes across the life span.
4. Random variations during development in cell number and organ architecture.

It still surprises that less than 35% of individual differences in longevity are heritable (Line 1), not only in human twins but also in laboratory models under tightly controlled environmental conditions (5–7). Even before birth and continuing throughout life, individuals accrue random endogenous damage to somatic nuclear and mitochondrial DNA and proteins from free radicals and nonenzymatic glycation that are irreducible by-stander effects of basal aerobic metabolism (Line 2). In addition, there is exogenous damage to somatic DNA and proteins accrued from the external environmental hits (Line 3). Thus, even with identical genes, individual organisms become mosaics of different cell and molecular damage. Lastly (Line 4), individuals with the same genome develop differently because random variations arise in cell numbers through the stochastics of cell fate and during cell migration, resulting in different individual organ structures (6,8). This is vividly demonstrated in *Caenorhabditis elegans*, in which young adult worms in the same culture dish show a wide range of individual variation in rates of swimming, eating, and egg laying as well as life span (8). These simple observations can help calibrate expectations for genetic associations with individual human aging processes and life expectancy.

Miller's (9) broad overview asks basic questions about its nature that merit revisiting by all researchers. The success of searches for genes against aging depends on how aging is defined. The popular animal models of flies, worms, and mice have yielded a rich harvest of specific gene mutations that increase life span and slow particular aspects of aging in multiple cells and tissues. Moreover, the domestic dog, though not widely used for aging studies, shows major variations between breeds in life span and rates of aging. However, so far none of these genes has shown strong association in human populations with specific age changes or life span. Miller argues: "the key question here is not 'are there genes for aging?', but rather 'how do genes postpone aging'." Further emphasis is needed, according to these arguments, on the mechanisms by which single mutations postpone in parallel aging changes in many tissues with different levels of cell replacement (eg, brain vs bone marrow). Miller's essay is at the outset intended to be provocative rather than a consensus statement, and we thank him for that risk-taking.

Tissenbaum (10) reviews connections among aging, longevity, and health span, with a focus on her laboratory

model of the nematode *C. elegans* mutants. More than 200 genes have been identified that alter life span and rates of aging, including many that have recognized importance in the life span of other models. Some of these genes also are on pathways that are influenced by caloric restriction, anticipating the long-sought synthesis of physiological, and genetic analysis of aging. Relationships to development are also being extended beyond the dauer-larva pathways that were so important in the early stages of life-span genetics in *C. elegans*. Although the role of these genes in human aging is still emerging, their link to basic functions such as declining body movements during aging has stimulated important work on the worm as a frailty model. Detailed cell and ultrastructural analyses of aging worms is at last being done and shows important similarities to mammalian aging in muscle, gut, and brain cells. Human neurologic diseases are also modeled with human transgenes for Alzheimer's, Huntington's, and Parkinson's diseases, with important prospects for easier manipulation than in the mouse models. An argument is developed for defining the health span of worms as a model for interventions by genetics and pharmacology which outlines the important issue of whether life-span extension "results in extension of healthy aging."

Although technical capability to determine individual genetic markers related to conditions of aging in human populations has proliferated, heritability continues to be a starting point for the search for genetic effects. However, at this point, there is clear recognition that the early approaches to separating genes and environment were too simplistic (11). It is now recognized that heritability is determined not just by genes and environment but by interactions between them as well as interactions within genetic attributes and environmental conditions. Causation is complex in that the environment one lives in may be heavily influenced by genetic characteristics (12). Estimates of heritability are also recognized as sensitive to context, as they depend both on the population characterized and the environmental and genetic characteristics of the population. Genetic effects may vary across environments leading to differences in estimates of heritability (13). Given these caveats (14), note that the more heritable a condition, the more likely that associated genes will be found.

Murabito and colleagues (14) present results on heritability of a variety of age-related health outcomes from both familial studies, including the Framingham study and the Long-Lived Family Study, and population studies. Their results are striking in that the estimates of heritability of so many age-related phenotypes are roughly similar: age at death, morbidity-free survival, and frailty. As one would expect, the estimates that they provide for less complex outcomes are somewhat higher: grip strength, walking speed, reproductive aging, bone mineral density, and Alzheimer's disease. This assessment of heritability across such a wide range of phenotypes linked to aging is suggestive of inheritance of an "aging" phenotype more generally.

Progress has been limited in identifying individual single nucleotide polymorphisms (SNPs) related to longevity, a complex phenotype with modest heritability (14). The Murabito and colleagues (14) article identifies only six SNPs linked to longevity with replicability from candidate gene and GWA studies. They describe the cooperative approach of the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium in examining the association of survival past age 90 with many more candidate genes (273) in a very large sample; however, none of these markers achieved GWA significance. The two genetic markers that link to survival with replicability from candidate gene studies are FOX03a and ApoE alleles. ApoE alleles are, perhaps, the most consistently and strongly related to a variety of aging outcomes. These findings recall those of (15) who use case-control and longitudinal studies and identify associations between longevity and genetic variation in ApoE and alleles related to IL-6, heat-shock proteins, and cholesteryl ester transfer protein. It is curious that ApoE SNPs are not included on some of the most frequently used chips for GWA studies.

This may be the time to address the appropriate methods for dealing with assessing the role of many alleles with small effects on complex traits like longevity. Yashin and colleagues (16) conclude that it is inappropriate to eliminate from further consideration many alleles because of low individual predictive value when these effects should be considered in concert with other alleles with small effects. They consider the effect on longevity of 169 alleles chosen with a less stringent exclusion rule from a GWA of the Framingham sample. When considered together, the effect of these alleles is "substantial and significant." Using a replication sample, they then identify 39 overlapping alleles and use those to predict 19% of the variance in life span. They suggest that relaxation of inclusion rules might be appropriate for analyses of the effect of many genes with small effects.

Melzer and colleagues (17) focus on what we know about robustly associated genetic influences on age-related diseases from GWA studies of relatively large samples, assuming delayed disease onset is reflective of a slower aging process. First, they note the success of GWA studies in identifying five SNPS that account for 40% of the heritability of age-related macular degeneration. The number of SNPs and genes associated with delay are identified for four age-related diseases: Alzheimer's disease (28 SNPs and 11 genes), cardiovascular disease (75 and 42), prostate cancer (55 and 16), and type 2 diabetes (67 and 25). Interestingly, they note little duplication of related SNPs across diseases, ApoE-related SNPs being one exception. This allows them to conclude that these age-related diseases are complex polygenic traits, which may be separately inherited. One of the advances that this group notes is the ability to link the associated genes with biological pathways in order to begin to shed light on mechanisms. Importantly, Melzer and colleagues (17) note that over 98% of the SNPS associated with these four age-related diseases are in the noncoding

regions of the genome. This leads them to emphasize the role of gene expression. They report on the ability of six different messenger RNA probes to distinguish between young and old individuals in a recent study leading to hope for finding gene expressions markers of aging (18).

Christensen and colleagues (19) address the question of whether there was a trade-off between cancer risk and longevity such that low cancer risk is associated with reduction in longevity. Studies of both mice and human populations have suggested the hypothesis. Using a twin sample, they examine cancer incidence among twins with long-lived and shorter lived cotwins, and find no support for the hypothesis and conclude that familial factors influence cancer incidence and longevity similarly.

Identifying both specific environmental as well as genetic influences on human health is the ultimate goal of this research. The disentangling of genetic and environmental effects on successful aging though novel analytic approaches is proposed by Eaton and colleagues (20). Their framework suggests that personality plays a role connecting complex genetic and environment explanations with successful aging. They propose two approaches: cotwin control designs (21) and gene-by-environment interaction (G × E) designs to understand how individual characteristics, such as personality, might moderate both genetic and environmental influences on successful aging.

The disentangling of genetic and environmental interactions in large population studies of aging outcomes is only now beginning (22). Building on what has been done in the last decade, it is likely to proceed rapidly through continued involvement of groups like the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. The cooperative consortia approach has fundamentally changed the way science is being done in this area and has been a real impetus for rapid progress. One of the major issues in examining gene by environment interactions is going to be the comparability across studies of the measure of environment. Although a large prospective population study of genes and environment is clearly desirable (23,24), for those who study aging, it is important to be able to use existing cohorts who are already well on their way through the life cycle if we are to make progress in the next half century. Clearly, we have made progress in understanding how the genome affects health. At the same time, we have discovered how complicated the links are and how much more needs to be known.

Such progress is necessary to develop significant clinical applications from our knowledge of genetic and gene × environment influences on age-related outcome. Applications remain minimal at present (17,25) describe some applications and conclude on a positive note that that identifying SNPs related to disease will result in more health care applications in the near future including new drug targets, better identification of disease, and other more specified treatments.

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