infoaging guides

BIOLOGY OF AGING

LONGEVITY

An introduction to aging science brought to you by the American Federation for Aging Research

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Researchers believe that your longevity, that is, the duration of your life, may rely on your having longevity assurance genes. Genes are the bits of DNA that determine an organism's physical characteristics and drive a whole range of physiological processes. Longevity assurance genes are variations (called alleles) of certain genes that may allow you to live longer (and perhaps more healthily) than other people who inherit other versions of that gene.

WHY ARE LONGEVITY ASSURANCE GENES IMPORTANT?

If scientists could identify longevity genes in humans, in theory, they might also be able to develop ways to manipulate those genes to enable people to live much longer than they do today. Slowing the aging process would also likely delay the appearance of age-related diseases such as cancer, diabetes, and Alzheimer's disease and therefore make people healthier as well.

Most longevity assurance genes that have already been identified in lower organisms such as yeast, worms, and fruit flies act to increase lifespan and grant resistance to harmful environmental stress. For example, scientists have identified single gene variantions in roundworms that can extend lifespans by 40 to 100 percent. These genes also allow worms to withstand often fatal temperature extremes, excessive levels of toxic free radicals (cellular waste products), or damage due to ultraviolet light.

Some of the longevity assurance genes in lower organisms have similar counterparts among human or mammalian genes, which scientists are now studying. While researchers have not yet found genes that predispose us to greater longevity, some have identified single human gene variants that seem to have a protective effect against certain age-related diseases and are associated with long life. For example, inheriting one version of a gene for a particular protein called apolipoprotein E (Apo E) may decrease a person's risk of developing heart disease and Alzheimer's disease. Identification of genes that prevent or delay crippling diseases at old age may help us find novel strategies for assuring a healthier, longer life, and enhancing the quality of life in the elderly.

HOW MUCH OF LONGEVITY IS GENETICALLY DETERMINED?

By some estimates, we humans have about 25,000 genes. But only a small fraction of those affect the length of our lives. It is hard to imagine that so few genes can be responsible for such a complex phenomenon as longevity. In looking at personality, psychologists ask how much is nature, that is, inherited, and how much is nurture, which means resulting from external influences. Similar questions exist about the heritability of lifespan. In other words, just how much of longevity is genetically determined and how much it is mediated by external influences, such as smoking, diet, lifestyle, stress, and occupational exposures?

Studies do show that long-lived parents have long-lived children. Studies of adoptees confirm that their expected lifespans correlate more strongly to those of their birth parents than those of their adoptive parents. One study of twins reared apart suggests about a 30 percent role for heredity in lifespan, while another says the influence is even smaller.

Some scientists estimate the maximal lifespan of a human to be approximately 120 years, a full 50 years longer than the Biblical three score and ten (Psalms 90:10). The people who have actually achieved that maximum can be counted on one hand—or one finger. Mme. Jeanne Calment of France was 122 years old at her death in 1997. But although few challengers to her record exist, we are seeing more and more members of our society reach 100. In fact, in the United States today, there are more than 60,000 centenarians, and their ranks are projected to grow to nearly 1 million by 2050. Much of this growth will be due to the convergence of the large aging Boomer demographic and improvements in health and medicine.

Most people who get to 100 do so by avoidance. They shun tobacco and excess alcohol, the sun and pollutants, sloth, bad diets, anger, and isolation. Still, many of us may know at least one smoking, drinking, sunburnt, lazy, cantankerous recluse who has lived to 100—and wondered how he or she did it.

More and more, scientists are finding that part of the explanation lies in our genes. The siblings of centenarians have a four times greater probability of surviving to age 90 than do siblings of people who have an average life expectancy. When it comes to living 100 years, the probability is 17 times greater in male siblings of centenarians and eight times greater in female siblings of centenarians than the average lifespan of their birth cohort.

On the flip side, we humans carry a number of genes that are deleterious to our health and longevity. These genes increase our risk for heart disease and cancer, as well as age-related but harmless symptoms such as gray hair and wrinkles. Though we cannot change our genetic pedigrees, perhaps if we know what unhelpful genes we carry, we can take steps, such as ridding ourselves of bad health habits and adopting good ones, that can overcome the disadvantages our genes confer and live as long as those people with good genes.

WHAT WE HAVE LEARNED FROM LOWER ORGANISMS

Our understanding of genes and aging has exploded in recent years, due in large part to groundbreaking work done in simpler organisms. By studying the effect of genetic modification on lifespan in laboratory organisms, researchers now provide fundamental insights into basic mechanisms of aging.

These include:

- Yeast
- Worms
- Fruit Flies
- Mice

Yeast

Researchers have identified more than 100 genes in baker's yeast (Saccharomyces cerevisiae) that are associated with increased longevity, and even more provocatively, have found human versions of many of these genes. Further study is ongoing.

As with all other organisms tested, researchers have reported that restricting the amount of calories available to yeast, either through reducing the sugar or amino acid content of the culture medium, can increase lifespan. Caloric restriction does not extend lifespan in yeast strains lacking one of the longevity assurance genes, SIR2. This result has been shown in multiple organisms from yeast to flies, and even in mice. The SIR2 protein is the founding member of the sirtuin family involved in genomic stability, metabolism, stress resistance, and aging. Researchers have found that overexpression of Sir2 extends lifespan, first in yeast as well as in worms and flies. Recently, the

conserved nutrient sensing TOR (Target of Rapamycin) pathway is emerging as a key regulator of lifespan and healthspan in various organisms from yeast to mammals. Tor1 is the yeast homolog of the mammalian target of rapamycin (mTOR) kinase, and Sch9 is a homolog of S6 kinase. Inhibition of Tor1 and Sch9 genes mediates effects of caloric restriction on the extension of lifespan in yeast. These results suggest common genes and pathways regulate lifespan in many organisms. Many labs are currently studying the mammalian homolog of these conserved genes to understand their importance in aging and a variety of age-related diseases. Determining how they interact with each other in yeast and whether they affect mammalian aging are important future experimental directions.

Worms

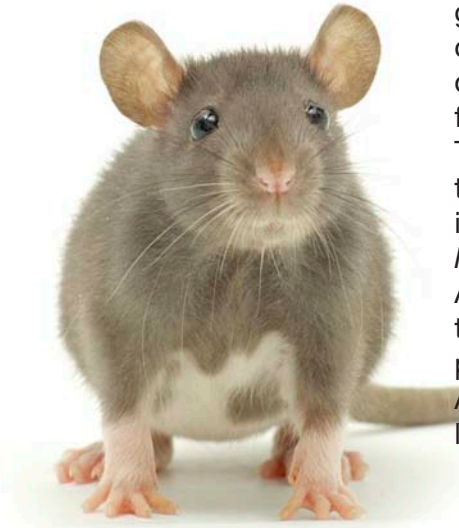
Caenorhabditis elegans, a roundworm that lives about three weeks, has been used extensively as a model for genetic studies of aging. The importance of insulin-like signaling as a key longevity pathway was established largely through studies in *C. elegans*, beginning with the initial observations that a mutation of certain chemicals in the body (PI-3-kinase age-1 or the insulin-like receptor daf-2) can double the lifespan of this animal.

As in other organisms, dietary caloric restriction has been shown to extend lifespan in *C. elegans*. A variety of different methods for inducing lifespan extension from dietary restriction have been described in *C. elegans*, including genetic models that eat less food, bacterial dilution (*C. elegans* eats bacteria and other microorganisms), and even complete removal of bacterial food during adulthood.

A particularly powerful feature of *C. elegans* for longevity studies is the ease with which the ability of genes to make functional gene products can be "knocked-down," that is, reduced, in this organism. So far hundreds of genes that affect lifespan have been identified.

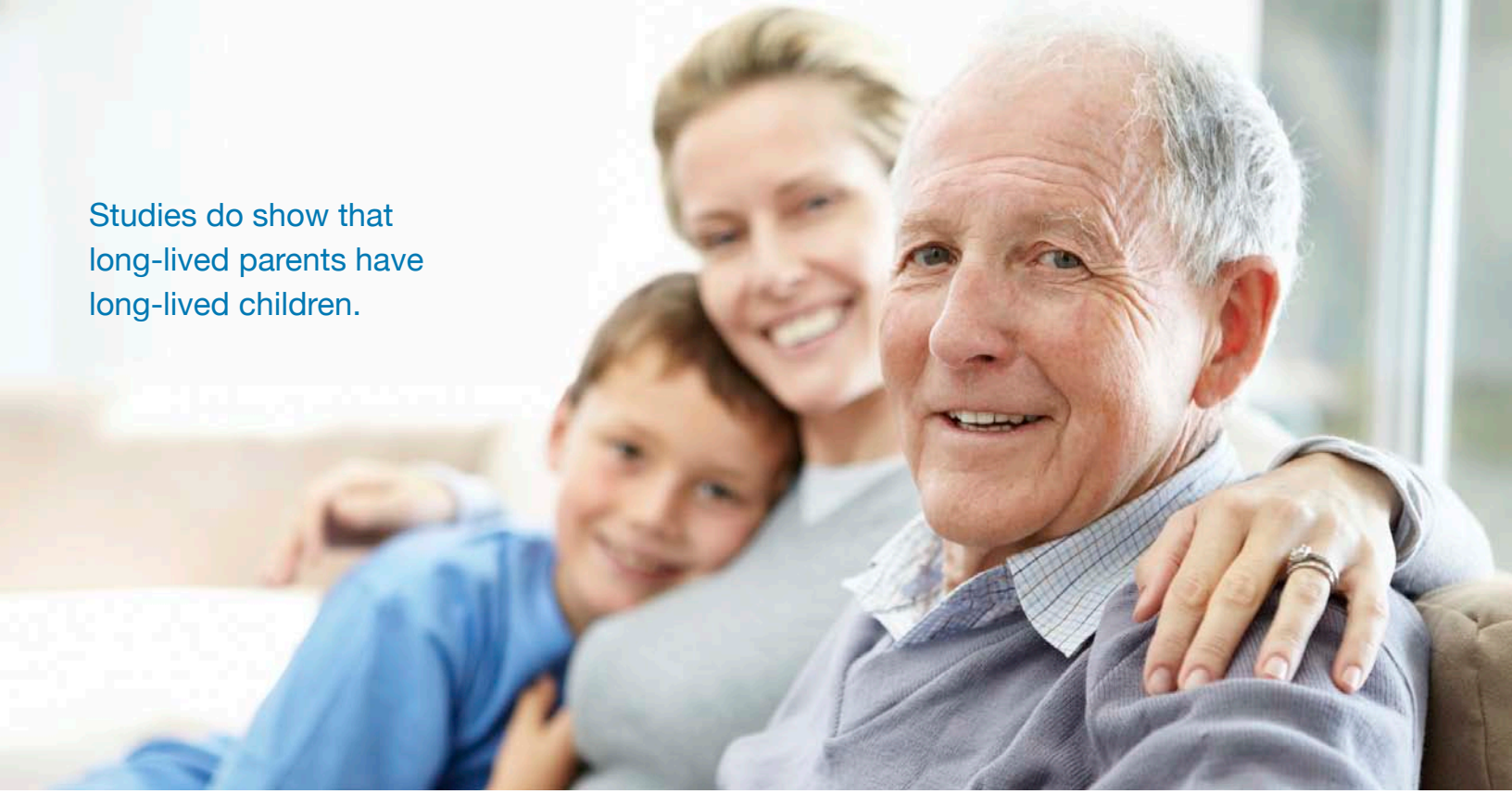
Fruit flies

Drosophila melanogaster, a slightly more complex organism than the roundworm, shows evidence of a more complex pattern of heritable longevity. Researchers have identified a gene they have named Methuselah, which increases lifespan in fruit flies by 35 percent. The Methuselah gene grants enhanced resistance to stress from heat and oxidative damage. In the April 2001 issue of *Science*, scientists described a gene, called Chico, that is active in the metabolism of insulin, which is important in determining fruit fly lifespan. Those fruit flies with mutations in both copies of the chico gene live an average of 48 percent longer than ordinary flies, and those with only one copy of the mutated form live an average of 36 percent longer. Researchers have noted that long-lived flies have increased stores of glycogen (needed for energy production) and fats, reserves for times when food is scarce or great amounts of energy are required. Genes that enhance the flies' ability to withstand oxidative stress also lengthen their lifespan. *Drosophila* was the first organism where the nutrient dependent effects of a molecular pathway called TOR on lifespan were first uncovered. The TOR pathway is critically important for mediating the longevity effects of caloric restriction in flies. TOR integrates signals originating from changes in growth factors, nutrient availability, energy status, and various physiological stresses. Other scientists have identified genetic traits in fruit flies that shorten lifespan. These genes reduce flies' ability to combat the damage of free radicals, the byproducts from the breakdown of oxygen, do to their cells. Therefore, in all three commonly studied non-mammalian organisms, resistance to stress correlates with long lifespan. This may represent a common element in aging, regardless of the organism.



Mice

With the ultimate focus on advancing human health, testing genetic modifications in mammals is critical and mice are often studied in aging research. The Ames dwarf mouse is a strain that has an inherited defect in the development of the pituitary gland, which means that this mouse does not secrete growth hormone. The absence of growth hormone results in defective transcription of the gene for an insulin-like growth factor. These genetic changes increase the mouse's lifespan. Reporting in the November 2001 issue of *Nature*, researchers attributed the Ames mouse's longer lifespan to mutations in a gene they call prop-1. Calorie restriction of the Ames mouse results in an even longer lifespan.



Studies do show that long-lived parents have long-lived children.

A number of genetic modificiations have been reported to increase the lifespan of mice. For example, "knocking out" or deleting a gene called p66shc in mice results in greater stress resistance and increased lifespan. As discovered in laboratory animals, reduced function of several genes involved in the insulin like signaling pathway increase lifespan and health span in mice. Scientists have also identified genes in mice that shorten lifespan. Many of these genes belong to DNA repair pathway, defects of which can cause premature aging and shorter lifespan in mice. DNA damage accumulates with age and better maintenance of the genome (fundamental genetic structure) by DNA repair mechanisms is likely to assure healthy aging and longevity. The most well-known protein implicated in genome maintenance is 53, referred to as guardian of the genome. While enhanced activity of p53 can prevent tumor development, it can also accelerate the aging process. This finding suggests that gene products such as p53 might have a trade-off, having good effects (cancer prevention) and bad ones (accelerated aging) at the same time.

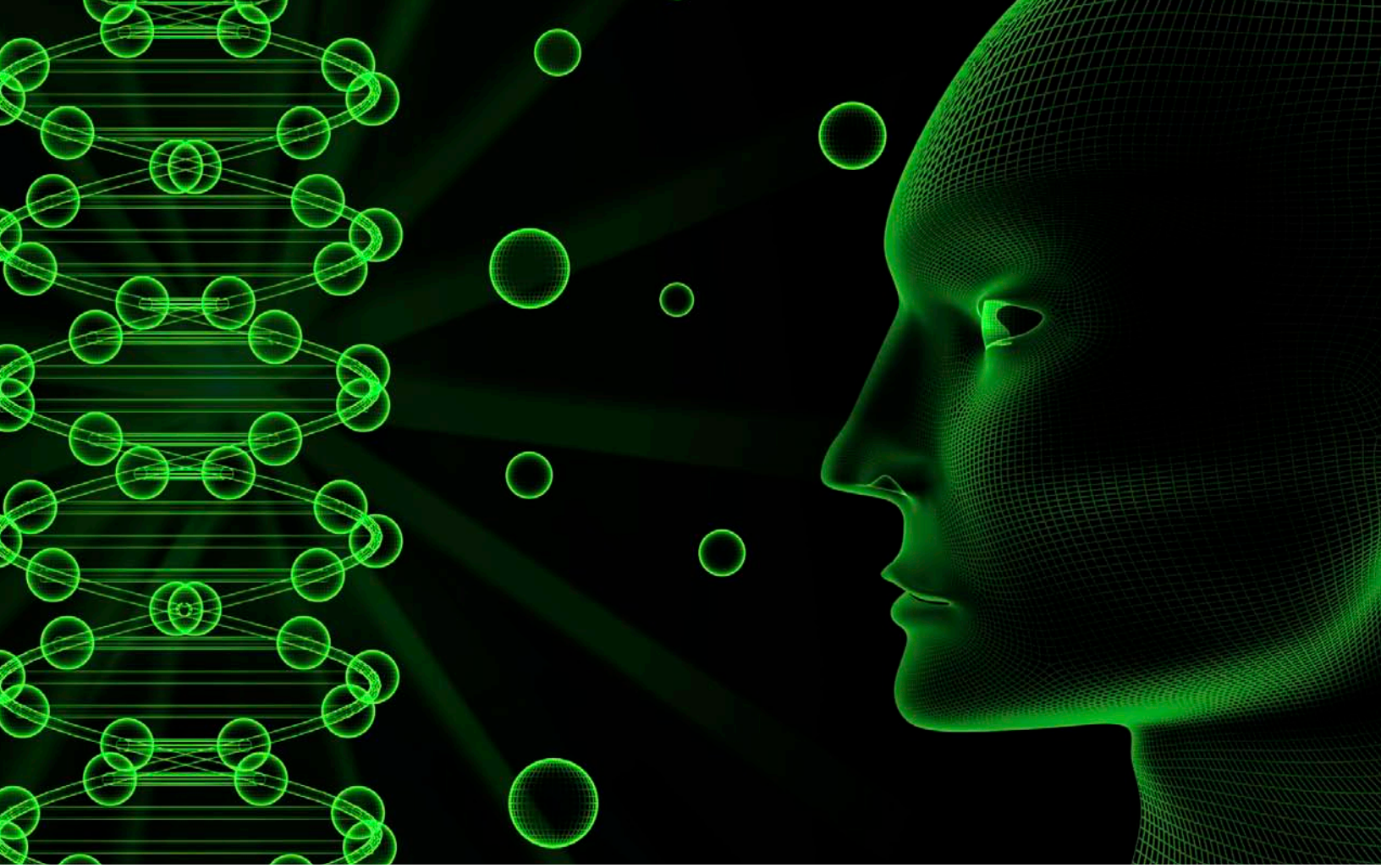
THE LATEST RESEARCH ON LONGEVITY ASSURANCE GENES IN HUMANS

Research into the genetics of human longevity has focused on:

- Genes that promote longevity
- Cell aging, cell death, and longevity
- Genes that accelerate aging

Genes that promote longevity
Several human genes have been identified that have an effect on longevity. Researchers at the University of California at Berkeley have identified some preliminary candidates for human longevity assurance genes. Certain genes in cell culture appear to permit those cultures to become immortal, that is, able to divide indefinitely without dying. For example, each time a cell divides, specialized DNA at the ends of chromosomes called telomeres shorten and the cell becomes more susceptible to dying. This shortening is compensated by the enzyme telomerase, which can repair the telomeres, preventing them from shrinking and extending the lifespan of cells. This suggests they may play a role in enabling tissues and organs to maintain their function, though they may also put cells at risk of becoming cancerous.

Cell aging, cell death and longevity
Human longevity research has also looked at genes involved in the cell aging process (how cells lose their ability to reproduce), as well as in apoptosis (the process by which cells are programmed to die). Both mechanisms, ironically, may play a role in increasing longevity. Cell death may be necessary, in part, to help clean out cells with genetic damage. If cells fail to die, cells with damaged genes can stick



Research into the genetics of human longevity has focused on genes that promote longevity, cell aging, cell death, and longevity and genes that accelerate aging.

around and cause problems (think of garbage left out for a few weeks or years). This can hasten aging and the appearance of age-related disease. In lower organisms genetic modification leading to reduced apoptosis extends lifespan. However, in mice this extension comes at the cost of increased cancer risk (see above describing mouse aging research). In humans, reduced activity of apoptosis may be beneficial to longevity as long as tumor development can be avoided.

Genes that accelerate aging

In an attempt to understand normal human aging and perhaps develop anti-aging targets, some investigators are looking at diseases of accelerated aging. One of the most familiar and well studied of these diseases is Werner's syndrome.

Werner's syndrome is a disease with properties similar to premature aging, and its symptoms don't begin until adolescence or later. Young people with Werner's syndrome develop gray, thin hair and wrinkles. They develop cataracts, diabetes, coronary artery disease, and unusual cancers. Researchers have linked Werner's syndrome to a specific gene. Scientists have found that mutations in that gene lead to abnormalities in DNA replication and repair of DNA damage. These abnormalities may lead to accelerated aging, as exemplified by the premature appearance of multiple symptoms of ageing in a growing family of human syndromes and in mice with genetic defects in DNA repair. Whether the abnormalities that lead to premature aging in human syndromes and mouse models are the same as those that lead to normal aging in seniors remains to be seen.

Longevity assurance genes and centenarians

Researchers around the world are looking at individuals who have lived a century in efforts to learn what makes them different from those whose lives are shorter. While no single factor has been identified to account for such longevity, most would agree that

centenarians have good genes and that they have avoided most toxic stressors, such as tobacco and excessive alcohol.

While a number of genes that shorten lifespan have been found, identifying the genes that lengthen lifespan is more difficult. Among the genes found in higher percentages among the oldest old are:

Apolipoprotein E (APOE): The E2 variant is more frequent in centenarians, while the E4 is half as common as in younger populations—which suggests, but does not prove, that those with the E4 gene die younger, while those with the E2 live longer. These results have been replicated in many other studies. In addition, the E4 variant confers increased risk of cardiovascular and Alzheimer's disease, while the E2 protects from these diseases, suggesting that APOE gene has major role in modulation of diseases of aging.

Forkhead box O 3 (FOXO3): The FOXO3 is an evolutionarily conserved human version of a C. elegans gene called DAF-16, a major regulator of lifespan in worms. FOXO3 appears to be the most robust longevity gene in humans, because common variants in this gene showed consistent association with longevity in multiple populations with different ethnic backgrounds, including Asians, Europeans, Caucasians, and African Americans.

HLA: The HLA genes relate to various immune functions. Certain variants have been found with greater frequency in centenarians than in younger populations. Some researchers suggest this may be due to better resistance to infection and inflammatory processes.

Dr. Thomas Perls, director of the New England Centenarian Study at Harvard Medical School, and his colleagues have been studying centenarians in the Boston area for several years. They have identified some lifestyle and personality factors that seem to contribute to longevity, but they have also found that there are about as many lifestyle and personality differences as there are similarities.

Dr. Perls and his colleagues have identified several families with many long-lived members. This supports the argument that at least some of longevity is indeed in the genes. Interestingly, two of those families have origins in the same area of Norway. This confirms what other researchers have noted: that some gene or genes present in high numbers in isolated populations may contribute to longevity.

One population that has remained isolated, at least genetically, is Ashkenazi Jews. Ashkenazi Jews are known to carry the genes for Tay-Sachs disease, a deadly disease in children, and the BRCA genes, associated with an extremely high risk of breast and ovarian cancer. But some members of this ethnic group are very long-lived. The relatively homogeneous genetic makeup helped identify the genes responsible for complex human traits, such as chronic diseases or longevity. Dr. Nir Barzilai, director of Institute for Aging Research and the director of the Nathan Shock Center of Excellence in the Basic Biology of Aging, Albert Einstein College of Medicine, pioneered the hunt for the human longevity genes by assembling and characterizing Ashkenazi Jewish families of exceptional longevity.

He and his colleagues have identified several biological markers and longevity genes that may explain how they have lived so long. These discoveries could lead to new drug therapies that might help people live longer, healthier lives and avoid or significantly delay age-related diseases such as Alzheimer's disease, type 2 diabetes, and cardiovascular disease.

LONGEVITY GENES AND AGE-RELATED DISEASES

A number of age-related diseases have been traced to particular versions of certain genes (called alleles). Many older adults who are free of these diseases have been found to possess the desirable, apparently disease-protective variants of those same genes. Thus, the same gene that in one form is a longevity assurance gene might in another form be one that shortens lifespan. Some age-related diseases with origins in our genes include:

- Heart Disease
- Cancer
- Neurological Disorders
- Macular Degeneration
- Osteoporosis

Heart disease

Three genes with effects on heart disease have been linked to human longevity. The most well-studied of these, called the apolipoprotein E (APOE) gene, produces a protein, apolipoprotein E (Apo E), that circulates in our blood. Researchers have found that those people who carry at least one copy of the E4 variant of the apoE gene have a higher risk of heart disease (and Alzheimer's

disease) than those who carry an E2 variant. Statistically, people who survive to age 100 have been found to be about half as likely to carry the E4 gene and somewhat more likely to carry the E2. Interestingly, investigators have found that people possessing two copies of the apparently protective E2 (i.e., one from each parent) have an increased likelihood of high blood triglyceride levels, a predictor for heart disease. This would seem to negate its protective effect.

A second gene with a known association with heart disease is the lipoprotein gene Cholesterol Ester Reverse Transferase (CETP), which moves cholesterol from peripheral tissues to the liver for excretion. A CETP gene variant associated with reduced levels of CETP activity and slightly protected carriers from developing coronary disease was found to be associated with human longevity.

Finally, Apolipoprotein C-3 gene (APOC3) keeps triglycerides from breaking down when they come into contact with water and has been implicated in coronary artery disease. APOC3 gene variants are linked to lower triglycerides, higher HDL-cholesterol, lower LDL-cholesterol in the blood, protection against heart disease, and greater longevity.

This research on the APOE, CETP, and APOC3 genes suggests that depending upon particular variants the same genes can have both positive and negative effects on specific diseases and aging in general. One version of the same gene can predispose people to diseases of aging, while another version of the same gene can lead to successful avoidance, delay, or survival of common age-associated medical conditions. These insights may also lead to novel preventive and treatment strategies for these diseases, which will have a profound impact on morbidity and mortality and will enhance quality of life in the elderly. For example, a drug modulating CETP action, which increases HDL cholesterol (typical traits in families with longevity), is in clinical trials, where it will be tested for its safety and effect on aging/longevity.

Cancer

While many cancers result from lifestyle and environmental risk factors (smoking, toxins such as asbestos and radon, repeated sunburns), scientists are uncovering an important role for genetics in both susceptibility and resistance to various cancers. Some examples are listed below:

Tobacco-related cancer: Worldwide, tobacco-related cancers cause up to 1,000,000 people to die every year. A large number of genes have been linked to lung cancer susceptibility. Among those linked to aging are the apoE gene, already investigated for its role in heart disease. Apo E also seems to play a role in susceptibility to cigarette-induced cancers. For example, researchers have found that those smokers who have survived into old age without cancer have a higher frequency of the protective E2 variant of the apoE gene.

Breast cancer: Breast cancer often occurs in two or more women from the same family, leading researchers to conclude that these women carry one or more "bad" gene alleles that promote cancer progression. Two genes, BRCA1 and BRCA2, are strongly linked to hereditary breast and ovarian cancer. It is estimated that women with one non-functional allele of BRCA1 have a 44 percent likelihood of getting breast or ovarian cancer by age 70. That number for BRCA2 is 27 percent. There are clearly other alleles that predispose women to breast cancer that are yet to be identified.

Colorectal cancer: This is one of the most common cancers worldwide. About 5 percent of the population will develop colorectal cancer late in life. It is estimated that approximately 20 percent of the cases of colorectal cancer can be attributed to hereditary influences and some of the responsible genes have been identified.

A major gene linked to susceptibility of many cancers is called p53. In humans, a p53 gene variant has been linked to increased mortality from cancer, while the same variant has been shown to increase survival time in old age, as it also did in mice studies. This finding suggests that gene products such as p53 might have a trade-off, having good effects (cancer prevention) and bad ones (accelerated aging) at the same time.

Neurological disorders

Alzheimer's disease: Early onset familial Alzheimer's disease arises before age 60. Mutations in genes for proteins called presenilins are responsible for 50 percent of familial Alzheimer's disease. Alzheimer's disease that comes on after age 60 is associated with the same E4 variant of apolipoprotein E gene that increases the risk of heart disease. Recently, the longevity CETP gene variant was linked to lower risk for dementia and Alzheimer's disease.

Cognitive function: The gene for APOE appears to affect cognitive function among elderly people who smoke or drink. Possession of the generally less helpful E4 variant seems to decrease the risk of cognitive decline among smokers and light drinkers, while increasing cognitive decline among heavier drinkers. Similarly the longevity CETP gene variants was linked to higher cognitive function, suggesting that longevity genes may alter risk for dementia and cognitive decline.

Stroke: Mice that inherit the undesirable E4 version of the apoE gene have an increased risk of stroke. In other animal studies, researchers have found that genes play a role in recovery from stroke. Older rats with deliberately induced strokes have less ability to turn on the genes that could promote recovery than younger rats also induced to have strokes. In human studies, genes that are likely to predispose individuals to stroke include APOE, ACE, and nitric oxide synthase.

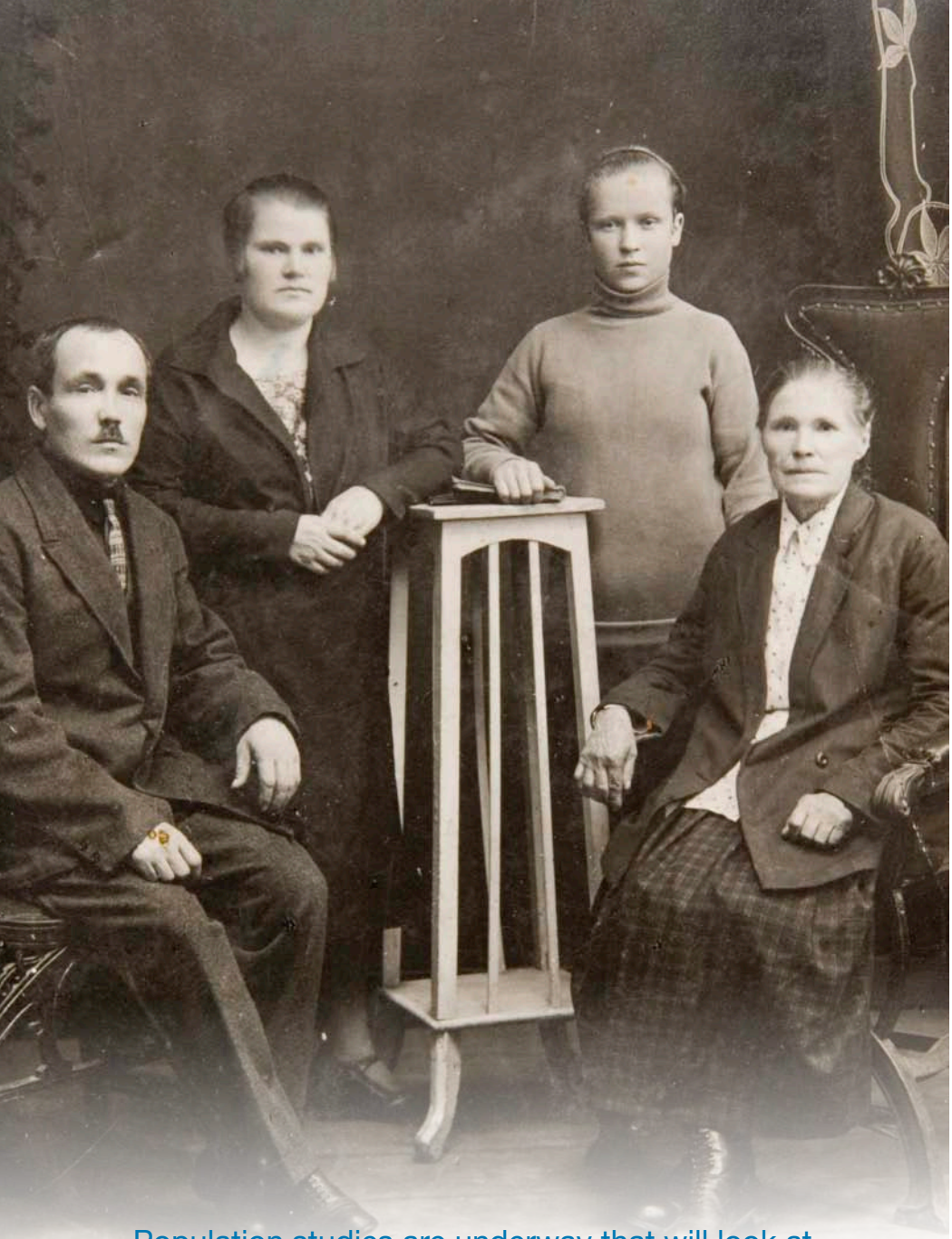
Macular degeneration
Age-related macular degeneration is thought to be the most common cause of loss of visual ability in the developed world. Several genes have been linked to the disease, but the genetics of the disease remain poorly understood. One known gene, our old friend ApoE and its E4 variant, confers dangerous and protective effects on various age-related processes, including macular degeneration. For example, macular degeneration, the leading cause of age-related blindness, occurs less frequently among those with the E4 variant of APOE.

Evidence suggests that there is a strong genetic component to osteoporosis.

Osteoporosis
Evidence suggests that there is a strong genetic component to osteoporosis; however, susceptibility is not thought to be linked to one gene. Rather, alleles of various genes in combination are thought to be important. This has made identification of genes more difficult. However a few genes have been identified, including the vitamin D receptor, the gene for type 1 collagen, and others. Again the ApoE gene may be involved. Postmenopausal women who have the ApoE4 allele suffer twice the rate of bone density loss and osteoporosis than women without the E4 variant. Of note, however, estrogen replacement therapy is equally effective in restoring bone mineral density in women with E4 or without it.

Mitochondrial genes and longevity
Mitochondria, the little organelles in our cells that serve as the cells' sources of energy, have their own genetic material, their own DNA, that we inherit. Some scientists have speculated that mitochondrial genes might play a role in longevity. They point out that mitochondria are the site of much of the oxidative metabolism that takes place in our cells, and they are therefore quite vulnerable to oxidative damage, the damage caused by free radicals that are the unfortunate byproduct of cell metabolism.

An ongoing study involving multiple research centers in Italy has looked at many facets of longevity. A report issued by some of the scientists involved in that study points out that certain patterns of mitochondrial gene inheritance could easily lead to improved longevity, if these mitochondria conferred more resistance to the damage of free radicals. Conversely, a less favorable group of mitochondrial genes might lead to decreased longevity. Preliminary findings from a study of more than 800 Italian men and women show that some mitochondrial gene variants are more common in centenarians. One such variant, labeled the J variant, was notably higher in centenarians. It will be interesting to determine whether cells with this mitochondrial DNA variant are more resistant to free radical damage.



Population studies are underway that will look at relatively genetically isolated groups of people, to determine which factors contribute to their longevity.

These same scientists looked at a gene pattern in the regular chromosomes that occur in the nucleus of the cells that predisposes to either longevity or shortened lifespan. This gene is called THO, and is a stress-responder gene. Some patterns of inheritance of THO variants favor longevity while others do not. The Italian researchers noted that some centenarians were found to possess the unfavorable version of THO, but that many of them also carried a favorable mitochondrial gene pattern, called the U haplotype. Therefore, variants of the THO gene may promote long lifespan in the context of some mitochondrial haplotypes but not in others. They concluded that there is more interplay between the nuclear and mitochondrial genes than had previously been realized in determining the genetic contribution to longevity.

Other Italian scientists are focusing on the genetic components of mitochondria that contribute to a shortening of lifespan. They note that certain mitochondrial gene patterns are associated with an increased likelihood of Parkinson's disease and Alzheimer's disease and may also affect the age of onset of Huntington's disease.

Other human longevity-associated genes

Insulin/insulin like growth factor-1 (IGF-1), a natural chemical in the human body that resembles insulin, may exert a powerful effect on lifespan. Researchers at the Albert Einstein College of Medicine discovered longevity-associated variants of a gene that acts as an IGF-1 gene receptor (a gene that allows cells to respond to particular chemicals) by studying Ashkenazi Jewish centenarians. These are rare variants (frequency is low in general population) but are nevertheless more frequent in centenarians.

Telomerase variants

Shorter telomere length has been associated with age-related diseases, among them coronary artery disease, hypertension, and dementia. Telomerase is an enzyme that can repair the telomeres, preventing them from shortening. Scientists from the Albert Einstein College of Medicine reported that Ashkenazi Jewish centenarian have telomerase variants linked to longer telomeres, better health, and longevity. Additional variants in the telomerase gene were discovered to be linked to telomere length. These results suggest that maintenance of telomere length may have an influence on health and aging in humans.

HLA variants
The HLA complex is a series of genes associated with the immune system. Certain inherited variants of the HLA system, known as ancestral haplotypes (a group of alleles on a single chromosome that are inherited together as a single unit), have been associated with longer life, particularly in males. Scientists in Bologna, Italy, reporting on a study of over 1,000 centenarians, found that the frequency of specific haplotypes varied between old females and males. They also reported that the ratio of females to males who survived to over age 100 ranged from about 2:1 in Sardinia to 7:1 in Mantova, a province in northern Italy. They found that male centenarians were generally healthier than their female counterparts and suggested that their results indicated that female longevity was less dependent on genes than was male longevity, and that women probably had healthier lifestyles and fewer toxic environmental exposures during their lifetimes.

THE FUTURE OF LONGEVITY ASSURANCE GENE RESEARCH

One interesting area for future research into the genetics of longevity will involve the study of the genes associated with blood lipids (cholesterol and its components) in the oldest old. Some of the oldest old have been found to have higher than average levels of HDL (the so-called "good" cholesterol that helps protect against heart disease). Researchers are now looking at their children, who are typically in their 70s, to see if their HDL levels are also higher than average and if they inherit similar versions of APOE and other genes thought to be related to lipid levels.

Population studies are underway that will look at relatively genetically isolated groups of people, to determine which factors contribute to their longevity. Scientists are looking for genes that confer protection against the common causes of death at younger ages as well as genes that confer increased survival. These include the Genome Wide Association Studies (GWAS), conducted in the New England Centenarian Study by Dr. Tom Perls; the Longenity Study of Ashkenazi Jewish Centenarians, conducted by Dr. Nir Barzliai; and the Leiden Longevity Study, conducted by Dr. P. Eline Slagboom.

Dr. Alan Shuldiner at the University of Maryland is studying the Old Order Amish who live in Lancaster, PA. The Amish are an isolated population, with few marrying outside their circle. Consequently, genes that govern longevity, or conversely, genes that govern premature deaths, should be amplified due to relative inbreeding. While Dr. Shuldiner and his colleagues have not uncovered any longevity genes as yet, they have identified a particular set of genes within the Amish population that is associated with high blood pressure and heart disease.

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