Association of FOXO3A variation with human longevity confirmed in German centenarians

The human forkhead box O3A gene (FOXO3A) encodes an evolutionarily conserved key regulator of the insulin-IGF1 signaling pathway that is known to influence metabolism and lifespan in model organisms. A recent study described 3 SNPs in the FOXO3A gene that were statistically significantly associated with longevity in a discovery sample of long-lived Japanese men of Japanese ancestry [Willcox et al. (2008) Proc Natl Acad Sci USA 105:13987–13992]. However, this finding required replication in an independent population. Here, we have investigated 16 known FOXO3A SNPs in an extensive collection of 1,762 German centenarians/nonagenarians and younger controls and provide evidence that polymorphisms in this gene were indeed associated with the ability to attain exceptional old age. The FOXO3A association was considerably stronger in centenarians than in nonagenarians, highlighting the importance of centenarians for genetic longevity research. Our study extended the initial finding observed in Japanese men to women and indicates that both genders were likely to be equally affected by variation in FOXO3A. Replication in a French centenarian sample generated a trend that supported the previous results. Our findings confirmed the initial discovery in the Japanese sample and indicate FOXO3A as a susceptibility gene for prolonged survival in humans.

EVOLUTION OF SENESCENCE

- Why do organisms age and die?
- SENESCENCE – deteriorative changes that occur in an individual with increasing age

SENESCENCE IS A LIFE HISTORY PHENOMENON

Life History: the stages of growth, reproduction, and dispersal that an individual goes through during its life from birth to death.
Senescence is a property of populations and species.

Senescence can be viewed as:

- A decline in age-specific survival probability
- A decline in age-specific reproductive rate

![Graphs showing mortality rates for Buboon and Lion](image)
The life history pacing of fertility completion is different in nonhuman primate species than in humans.

Alberts S C et al. PNAS 2013;110:13440-13445

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Figure 10.5 The "Y model" for trade-offs between somatic and reproductive function. (Modified from Tatar and Carey 1995 and de Jong and van Nordwijk 1992.)
EVIDENCE OF HERITABLE GENETIC VARIATION FOR LIFESPAN

![Graph showing average longevity (in years) over generations for late reproducing and early reproducing populations.](image)

EVOLUTIONARY EXPLANATIONS FOR SENESCENCE

- Antagonistic pleiotropy theory
- Mutation – Selection Balance theory

ANTAGONISTIC PLEIOTROPY THEORY

- Senescence occurs because of the pleiotropic effects of genes.
- Selection for alleles which enhance survivorship and/or reproductive rate at early reproductive ages may concomitantly lower survivorship and reproductive rates at later ages.
- There is a tradeoff (antagonism) between fitness components early in life and later in life.
EVIDENCE FOR ANTAGONISTIC PLEIOTROPY

LATE REPRODUCTION

EARLY REPRODUCTION

THE INTENSITY OF NATURAL SELECTION DECLINES WITH AGE

…the forces of natural selection weaken with increasing age …. If a genetical disaster… happens late enough in individual life, its consequences may be completely unimportant. Even in such a crude and unqualified form, this dispensation may have a real bearing on the origin of innate deterioration with increasing age.

Medawar, 1952

LATE-ONSET MUTATIONS ARE NOT ELIMINATED BY NATURAL SELECTION

EXAMPLE: Huntington’s chorea: disabling disorder of the nervous system caused by a dominant mutation that is not expressed until the age of 35 – 40.

George sumner huntington
MUTATION-SELECTION BALANCE THEORY

- Genetic variation is maintained by a balance between the input of variation by mutation at many gene loci and the loss of variation due to selection.
- Because selection is weaker at older ages, there is a higher equilibrium level of deleterious mutations with phenotypic effects that are expressed at later ages.
- This higher “genetic load” of late-acting deleterious mutations causes senescence.

HALDANE’S EQUILIBRIUM GENE FREQUENCY

Assume \( q \) is small, and \( u \gg v \):

- Selection against a completely recessive allele:
  \[
  \begin{align*}
  W_{AA} &= 1 \\
  W_{Aa} &= 1 \\
  W_{aa} &= 1 - s \\
  q^2 &\approx \frac{u}{s}
  \end{align*}
  \]

- Selection against a completely dominant allele:
  \[
  \begin{align*}
  W_{AA} &= 1 \\
  W_{Aa} &= 1 - s \\
  W_{aa} &= 1 - s \\
  q^2 &\approx \frac{u}{s}
  \end{align*}
  \]

FUTURE PROSPECTS FOR AGING RESEARCH

People who think they are going to find a fountain of youth, whether at the molecular level or at any level, are not going to be successful.

G. C. Williams

- Many evolutionary biologists feel that the theories of senescence predict that a medical “fountain of youth” is an unlikely prospect.
- Mutation selection balance theory, for example, suggests that late-acting deleterious genes should accumulate at many different loci making the prospect of finding a **single aging gene** impossible.
Sardinia’s Mysterious Male Methuselahs

Antonio Todde, age 112

MADAME CALMENT – AGE 122

I don’t feel old. I don’t feel anything until noon. Then it’s time for my nap.
- Bob Hope

Growing old gracefully
Across the industrialized world, birth rates are falling and people are living longer. This will require a new focus on research to promote healthy aging rather than simply treating the diseases of old age. Alice Abbott reports.
DEMOGRAPHIC PROJECTIONS FOR THE PERCENTAGE OF AMERICANS OVER THE AGE OF 65

- Probability that populations will reach a proportion of 1/3 of individuals > age 60
- Fraction of Western European populations > 80 years old

Lutz et al. Nature 2008

Research on Aging: Biggest Bang for the Buck?

We could certainly slow the aging process down if it had to work its way through Congress.

Will Rogers

“It is clear that directly targeting aging is theoretically superior to treating individual chronic diseases, but until recently, translational approaches to achieve this goal have been just that—purely theoretical.”

Healthy aging: The ultimate preventative medicine

EXTENDED LIFE-SPAN AND STRESS RESISTANCE IN THE DROSOPHILA MUTANT METHUSELAH

Lin et al., Science 1998
WERNER’S SYNDROME

Werner’s syndrome (WS) is a rare, autosomal recessive disease. Its symptoms are:

- Growth is deficient post-puberty
- Predisposition to arteriosclerosis, diabetes, non-epithelial cancers
- Premature ageing - wizened appearance, graying hair, hair loss

Cultured cells from patients show:

- Poor division
- Telomere shortening
- Karyotype changes
- Increased mutation rate

The gene was mapped in Japanese families by looking for regions of the genome that were homozygous in patients (because it is a recessive disease). The gene was isolated in 1996. It codes for a DNA helicase enzyme.

A RELATED SYNDROME “PROGERIA” MAY LEAD TO INSIGHTS INTO THE PATTERNS OF GENE EXPRESSION RELATED TO HUMAN AGING.
Mitochondrial DNA:

- Mutation rates in mtDNA are 10-20 times that of nuclear genes.
- Mitochondria are extremely metabolically active and are an O₂ rich environment.
- Leads to free radical damage. Deletion mutations in humans have been shown to increase with age.

Aging-Dependent Large Accumulation of Point Mutations in the Human mtDNA Control Region for Replication

FROM: Michikawa Science 1999

Mitochondrial dysfunction and longevity in animals: Untangling the knot

“There is no doubt that mitochondria wear down with age. However, by itself, this functional decline appears to be insufficient to cause aging.”

FROM: Ying Wang, and Sengfried Mole Sience 2010, doi: 12341.1234
CONTROL OF AGING BY THE INDY (I'M NOT DEAD YET) LOCUS


Long-lived Indy induces reduced mitochondrial reactive oxygen species production and oxidative damage


TELOMERASE RESEARCH IS A HOT TOPIC IN AGING AND CANCER RESEARCH

FAILURE OF CELL REPLICATION MAY BE DUE TO DAMAGE TO TELOMERES

- Telomeres are regions of highly repetitive DNA at the ends of chromosomes.
- They prevent the ends of chromosomes from joining together during replication.
- DNA polymerases are unable to fully replicate Telomeres.
- Telomeres shorten with each cell replication unless they are maintained by telomerase. Eventually the cell is unable to replicate and undergoes “replication senescence”.

Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians

PNAS 2009
Relationship of telomere attrition to human aging-related diseases. Telomere attrition is depicted as an underlying, shared, interactive contributor to the etiologies of aging and aging-related diseases. Because both nongenetic and genetic influences affect it, telomere maintenance is a malleable and integrative indicator of overall health.

“STARVATION” CAN ALSO CHANGE LIFE SPAN

![Graph showing survival patterns of different conditions](image)

**Figure 2.10**: Survival patterns of “normal” rats, fed ad libitum, and “retarded” rats, which were subjected to nutritional restriction that delayed reproductive maturation. Retarded rats live significantly longer. (From McCay, Swan, and Crow, 1932.)

WORKING OUT THE “STARVATION” PATHWAYS

*C. elegans* & *Drosophila*
Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans


Growth & reproduction → Increased longevity → Somatic maintenance

DNA damage → Apoptosis, Cell senescence

Transcriptional interference → Mutation, Altered chromatin

AGING → CANCER

“You wouldn’t put a $1000 crystal on a $5 watch”
- Steven Austad