

Human genetics of aging: the centenarians



A&S300-002 Jim Lund



Human lifespan

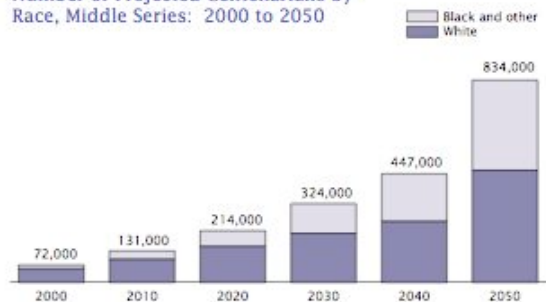


- Mean Longevity in the US:
 - Males, 74 yrs.
 - Females, 80 yrs.
- Maximum longevity (verified):
 - Jeanne Clament who died in 1997 at age 122

Increases in centenarian numbers



Figure 1.
Number of Projected Centenarians by Race, Middle Series: 2000 to 2050



Source: Day, J. C., 1996, *Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995 to 2050*, U.S. Bureau of the Census, Current Population Reports, P23-1130, U.S. Government Printing Office, Washington, DC.

Increases in centenarian and supercentenarian numbers



- Centenarians (100+ years)
 - 0.92% survive to 100 years in Japan, 13,036 centenarians.
- Supercentenarians (110+ years)
 - 153 known in the 18 developed nations (2000 statistic).

Millersburg, KY woman lived 114 years



Millersburg, KY woman lived 114 years

Grace Thaxton (1891-2005)

“Mrs. Thaxton was the fourth-oldest person in the country and the sixth-oldest in the world, according to the California-based Gerontology Research Group. Mrs. Thaxton and her mother also hold the record as the world's oldest mother/daughter combination, with a combined age of 223 years.”

“Mrs. Thaxton was active as she approached and passed 100 years, driving a car until she was 95 and hooking rugs until she was 103.”

“Mrs. Thaxton is survived by her son, Robert;”

7/8/2005 Lexington Herald-Leader

Early studies of aging heritability

Alexander Graham Bell (1918 study)

- Examined birth/death records of descendants of William Hyde (died 1681 in CT) over two centuries including almost 9,000 descendants.
- Long-lived parents tended to have long-lived children.

Other similar studies found the same thing:

- Chinese family 14th-19th century.
- Swedish families 1500-1829.

Heritability

| | | Trait | Heritability |
|----------------|----------------------|-------------------------|--------------|
| H=1 Genes only | H=0 Environment only | Clubfoot | 0.8 |
| | | Height | 0.8 |
| | | Blood pressure | 0.6 |
| | | Body mass | 0.5 |
| | | Verbal aptitude | 0.7 |
| | | Math aptitude | 0.3 |
| | | Spelling aptitude | 0.5 |
| | | Fingerprint ridge count | 0.9 |
| | | Intelligence | 0.5-0.8 |
| | | Total serum cholesterol | 0.6 |

Genetic Heritability of Human Lifespan

Cournil & Kirkwood 2001

Twin Studies

- McGue et al (1993) 0.22
- Herkind et al (1996) 0.25
- Ljungquist et al (1998) <0.33

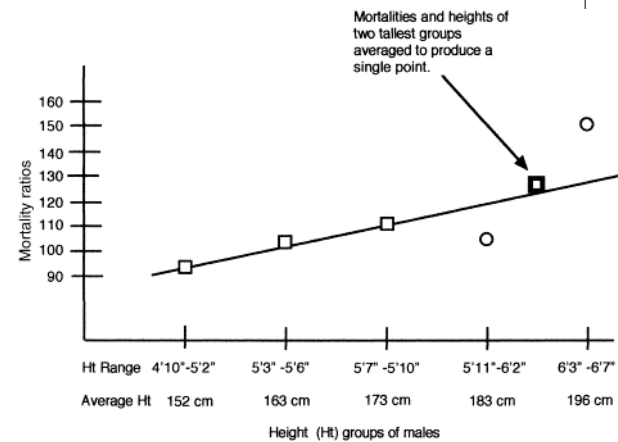
Traditional Family Studies

- Philippe (1978) 0-0.24
- Bocquet-Appel & Jakobi (1990) 0.10-0.30
- Mayer (1990) 0.10-0.33
- Gavrilova et al (1998) 0.18-0.58
- Cournil et al (2000) 0.27

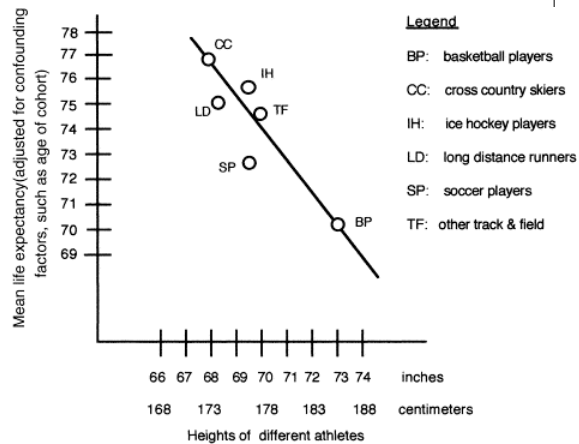
Genes account for 25% of what determines longevity



Predictors of longevity



Predictors of longevity



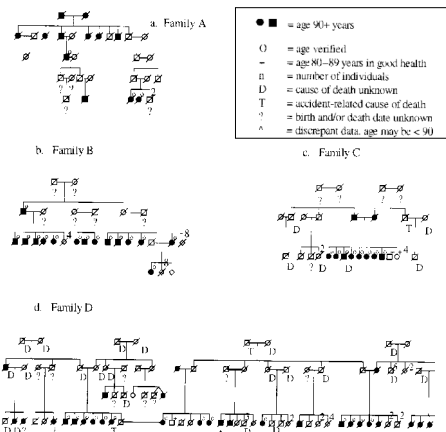
Long lived families

New England Centenarian Project

- Four families segregating genes for longevity.
- Pedigrees with multiple long-lived members across generations.



Long-lived families



Predictors of longevity

- Siblings of centenarians have higher survival, death rate 1/2 of normal cohort. (Perls et al., 2002)
- Parents of centenarians longer lived than average.
- 90% of centenarians living independently at age 90.

Dividing up the centenarians

Centenarians:

- “survivors”: diagnosis of age-related disease before age 80, survived it.
 - 24% of males, 43% of females.
 - “delayers”: diagnosis of age-related disease after age 80.
 - 44% of males, 42% of females.
 - “escapers”: live to 100 without any age-related disease.
 - 32% of males, 15% of females.
- **Most informative group for aging studies!**

(Evert et al., 2003)

Aspects of centenarian biology

Comparison of centenarians with adults of various ages:

- Lower body mass index (BMI).
 - Lower body fat.
 - Lower plasma triglycerides.
 - Lower oxidative stress levels.
 - Higher insulin sensitivity (less susceptible to type II diabetes.)
 - Higher plasma levels of active IGF-1.
- Barbieri et al., 2003, Paolisso et al., 1997.

Centenarian genetics



Absence of deleterious alleles of disease genes.

- Cancer, vascular disease, neurodegenerative disease, diabetes, etc.

Centenarians age evenly--no organ system is particularly susceptible to age-related disease and ages fast.

Centenarian genetics



Absence of deleterious alleles of disease genes.

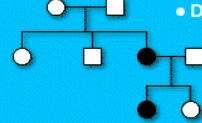
| | Children of centenarians | Controls |
|---------------------|--------------------------|----------|
| High blood pressure | 26% | 52% |
| Heart disease | 13% | 27% |

Approaches to Identifying Susceptibility Genes for Common Diseases



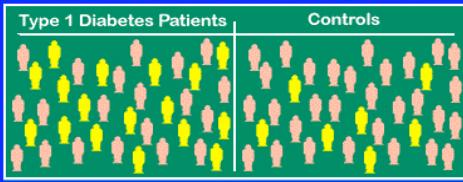
Linkage Studies:

- A relation between loci
- Done within families



Association Studies:

- A relation between alleles
- Done in populations

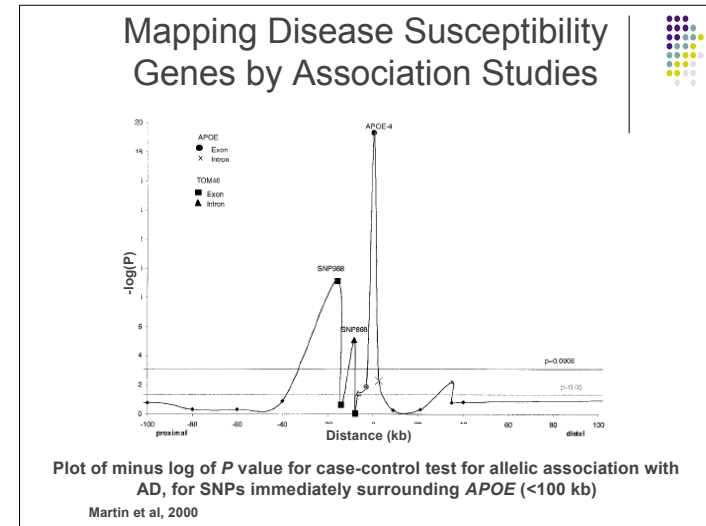
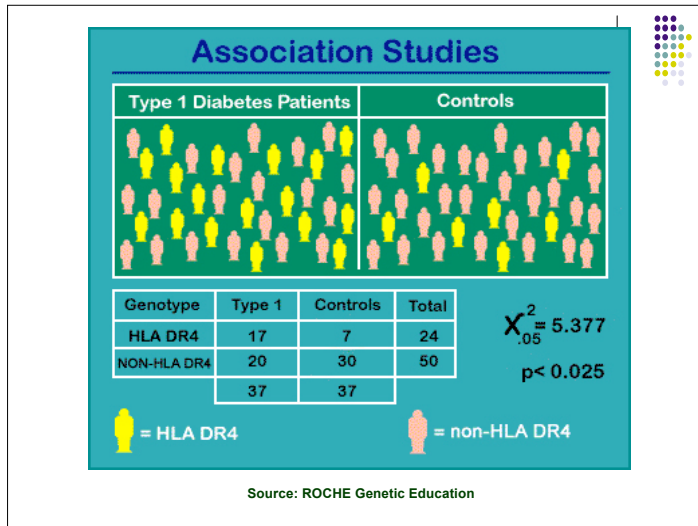


Source: ROCHE Genetic Education

Differences between linkage and association



| Linkage | Association |
|---|--|
| Linkage is a property of loci | Association is a property of alleles |
| Role: * To identify a biological mechanism for transmission of a trait * To locate the gene involved | Role: * To identify association between an allelic variant and a disease * To identify linkage disequilibrium between a disease allele and a marker |
| Coarse mapping (>1cM) | Fine mapping (<1cM) |
| No information about which allelic variant associated with higher risk of disease | |
| Require family pedigrees | Case-control or family based approach |
| Use very polymorphic markers | Usually bi-allelic markers |



Centenarian genetics, positive

Apolipoprotein E (ApoE)

- Study of French centenarians. 338 centenarians, controls aging 20-70.
- $\epsilon 4$ allele of ApoE, which promotes premature atherosclerosis, is significantly less frequent in centenarians than in controls ($p < 0.001$)
- Frequency of the $\epsilon 2$ allele significantly increased ($p < 0.01$).

Schachter et al., 1994

ApoE2 protects against cardiovascular disease and Alzheimer's disease.

Centenarian genetics, positive

Mitochondrial polymorphisms

- Study of 321 very old subjects and 489 middle-aged controls from Finland and Japan
- Three common inherited mitochondrial DNA polymorphisms (150T, 489C, and 10398G) promotes longevity.

Niemi et al., 2005

Reason for the association? Unclear.

IL-10 promoter polymorphism



Hypothesis: Genetic variations in pro- or anti-inflammatory cytokines might influence successful ageing and longevity. IL-10 is an appropriate candidate because it exerts powerful inhibitory effects on pro-inflammatory function.

- Study of 190 Italian centenarians (>99 years old, 159 women and 31 men) and in 260 <60 years old control subjects (99 women and 161 men).

- Matched for geographical distribution, genotype frequencies.

- 1082G homozygous genotype (associated with high IL-10 production) was increased in centenarian men ($P < 0.025$) but not in centenarian women.

- Anti-inflammatory IL-6 and IFN-gamma gene polymorphisms associated with longevity in other studies.

Lio et al., 2002

No association with IL-6, IL-10 seen in a Finnish study, Wang et al., 2001

Centenarian genetics



Negative/mixed results

Sirtuin 1, SIRT1 (negative)

Microsomal Transfer Protein (mixed)

Cholesteryl ester transfer protein, (mixed)

FOXO1A, IRS1, PIK3CB, PIK3CG, and PPARGC1A (negative)

INSR (mixed)

Catalase (mixed)

Angiotensin-converting enzyme 1 (ACE1) (mixed)

IL-6, IL-10 (mixed)

Centenarian genetics



INSR

- Study of 122 Japanese semisupercentenarians (older than 105) with 122 healthy younger controls.

- One INSR haplotype, which was comprised of 2 SNPs in linkage disequilibrium, was more frequent in semisupercentenarians than in younger controls.

Kojima et al., 2004

Other studies found no linkage, the linkage may be population specific.

Centenarian genetics



(PPAR)gamma-2

Peroxisome proliferator-activated receptor (PPAR)gamma-2 is an important regulator of adipose tissue metabolism, insulin sensitivity and inflammatory response.

- Study of 222 long-lived subjects and 250 aged subjects.

- Long-lived men had an increased frequency of Pro/Ala genotype (20% vs 8.5%).

- Subjects with Pro/Ala polymorphism had significantly lower BMI.

Barbieri et al., 2004

Centenarian genetics



The near future

SNP-based genome scans for association of genes/alleles and longevity

Unbiased approach--all genes are checked

May find genes associated with slower aging as well as disease prevention.