Announcements

- Course evaluation and survey
- Town hall meeting Aug 18, when where?
- Class picture after lecture
- Prize(s) for highest aging signature

Genetics of Aging

Genetics 210

Aug. 4, 2010

Stuart Kim, Dev. Bio. And Genetics

TABLE 1.1

Human Life Expectancy

Time Period	Average LIfe Expectancy (in years)
Prehistoric times	18
Ancient Greece	20
Middle Ages, England	33
1620, Massachusetts Bay Colony	35
19th century, England	41
1900, USA	47
1915, USA	54
1954, USA	70
1992, USA	75

Maximal human lifespan is about 100 years

Some notable elders

- Sophocles - Playwrite (wrote *Electra* at the age of 82)
  495 BC. lived to be +/- 90
- Hippocrates - Physician ("Father" of Modern Medicine)
  460 BC. lived to be 90 or 100

Top 10 Leading Causes of Death [*]

	Numbers of Deaths
1. Heart Disease	652,091
2. Cancer	559,312
3. Stroke (Cerebrovascular Events)	143,579
4. Chronic Respiratory Diseases (COPD)	130,933
5. Accidents (unintentional injuries)	117,809
6. Diabetes	75,119
7. Alzheimer's Disease	71,599
8. Pneumonia (Flu)	63,001
9. Nephritis, Nephrotic Syndrome, and Nephrosis	43,901
10. Septicemia	34,136

Ref.: CDC; National Center for Health Statistics (NCHS); 2005

*** Does not distinguish *intrinsic* vs. *extrinsic* causes of death, which blurs the distinction between Longevity-Determination Genes and Entropy.**

World's Oldest Human

Jeanne Calment of Arles, France

1855-1977

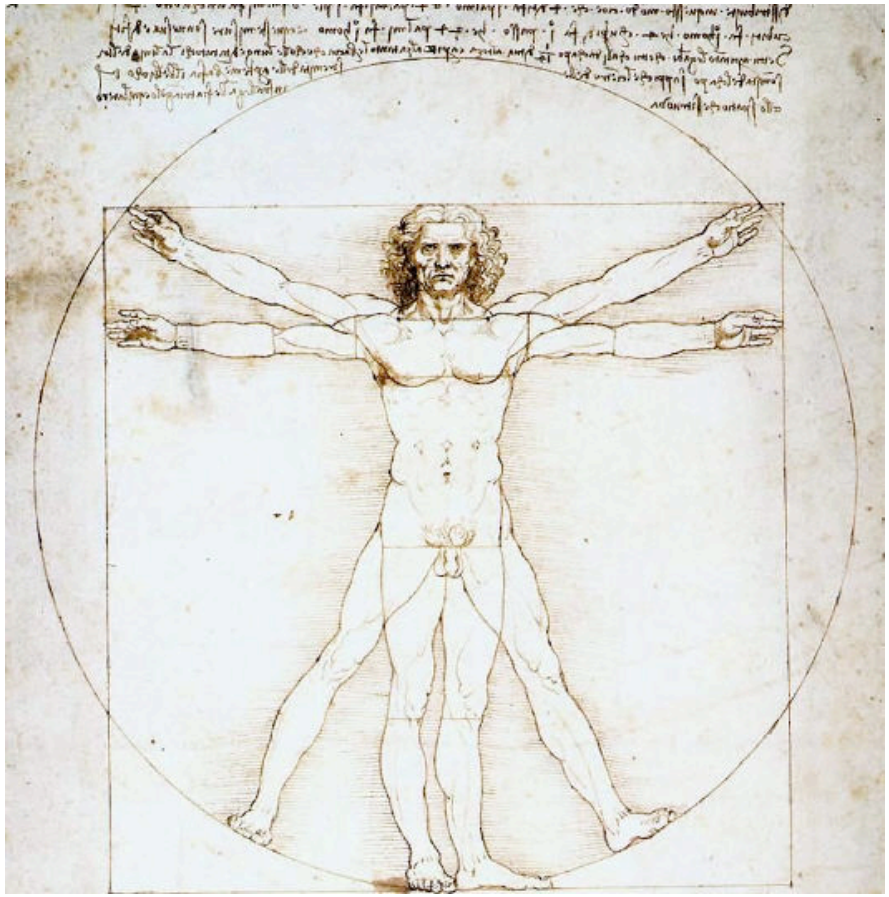
122 yrs

Reichert Family

From Gross L., 2006

Supercentenarian Genome Project

Stuart Kim (Stanford); Stephen Coles (SRF); Lee Hood (ISB)
David Galas (ISB)



Soledad Mexia, 50th oldest person in the world

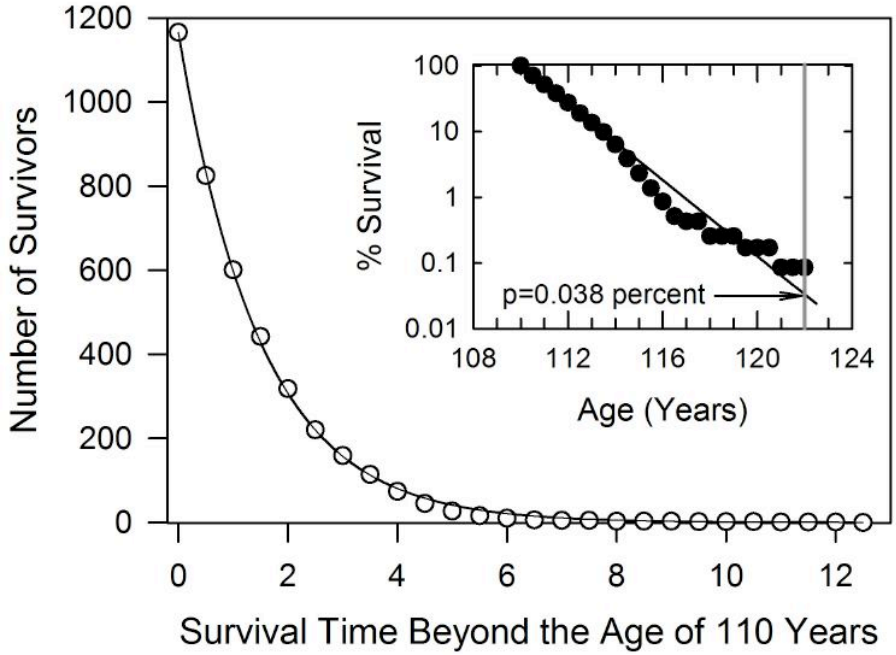
born Aug. 13, 1899, 110 yo

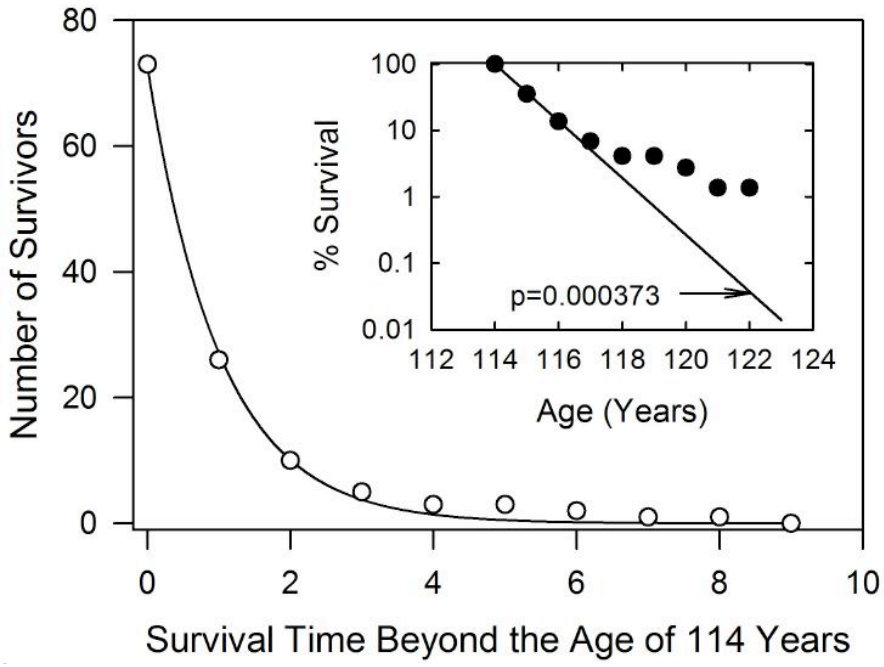
Numbers Surviving by Age

AGE	NUMBER
110	1166
110.5	825
111	601
111.5	442
112	318
112.5	220
113	159
113.5	114
114	74
114.5	45
115	27
115.5	16
116	10
116.5	6
117	5
117.5	5
118	3
118.5	3
119	3
119.5	2
120	2
120.5	2
121	1
121.5	1
122	1
122.5	0

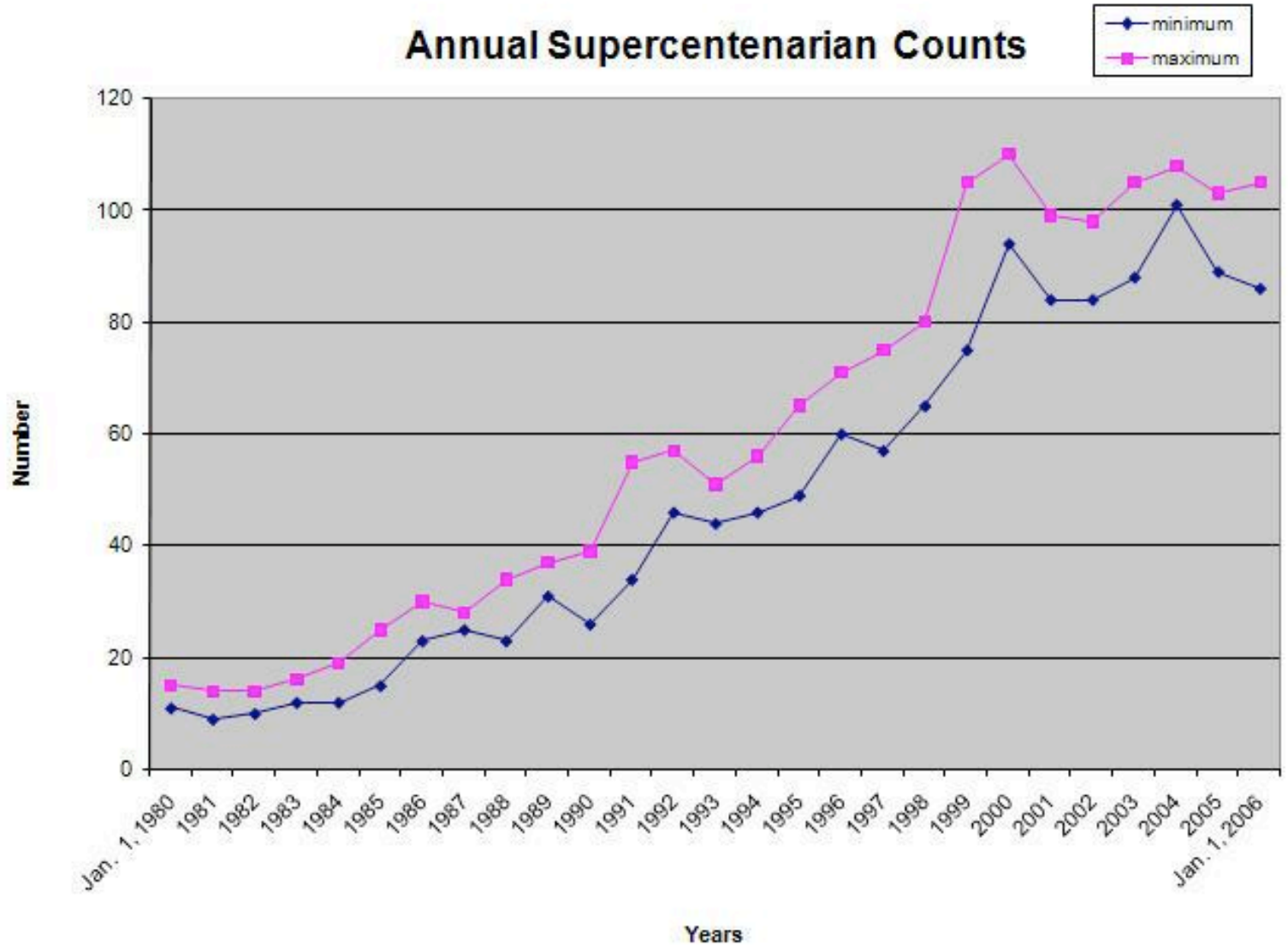
(data by Mr. Louis Epstein of New York)

Graphs by Greg Fahy, Ph.D
(January 19, 2010)

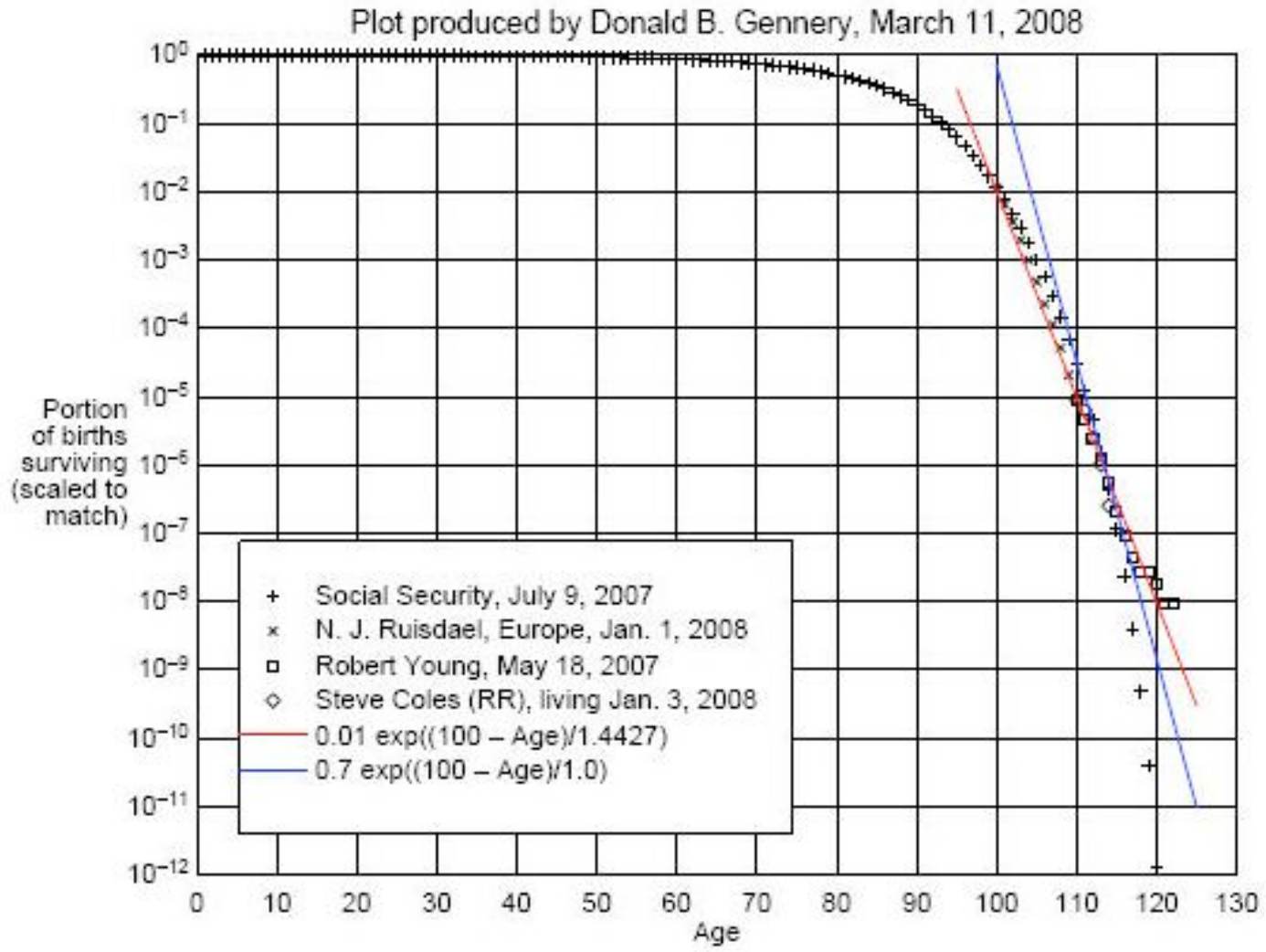




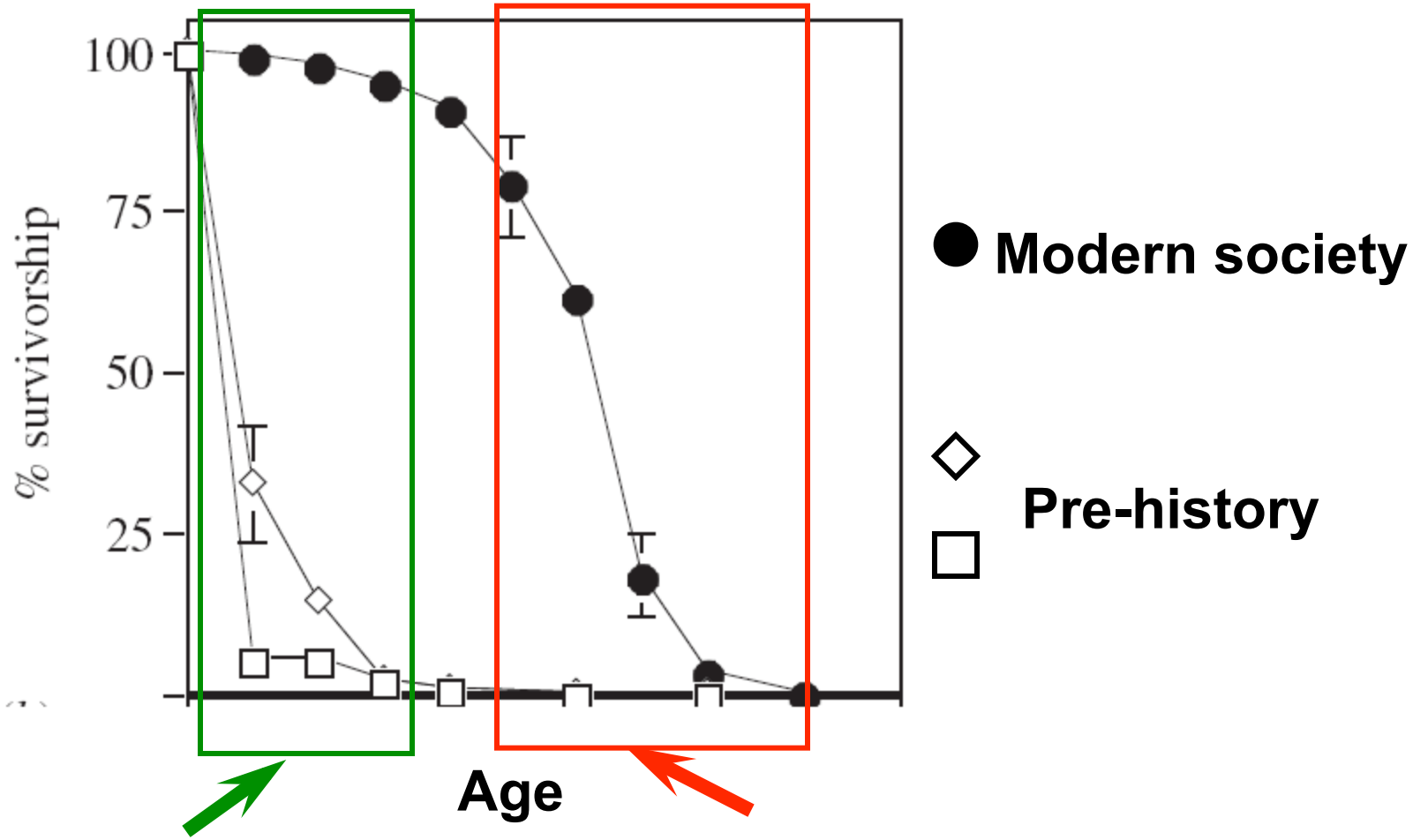
Numbers of Supercentenarians



Survival (Logistic Function)



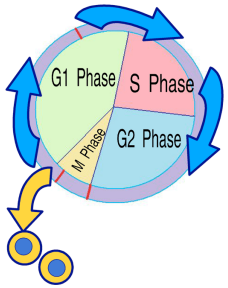
Aging: beyond the force of natural selection



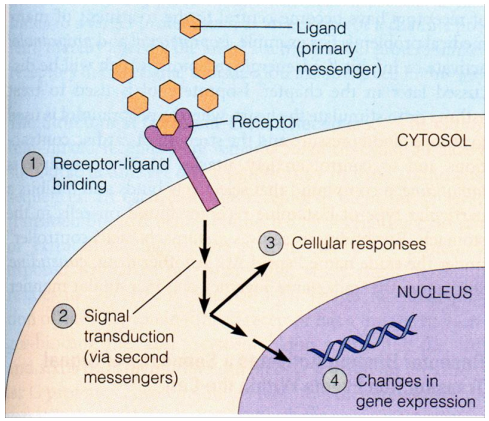
Aging is beyond the force of natural selection

Evolved Processes

Cell Cycle



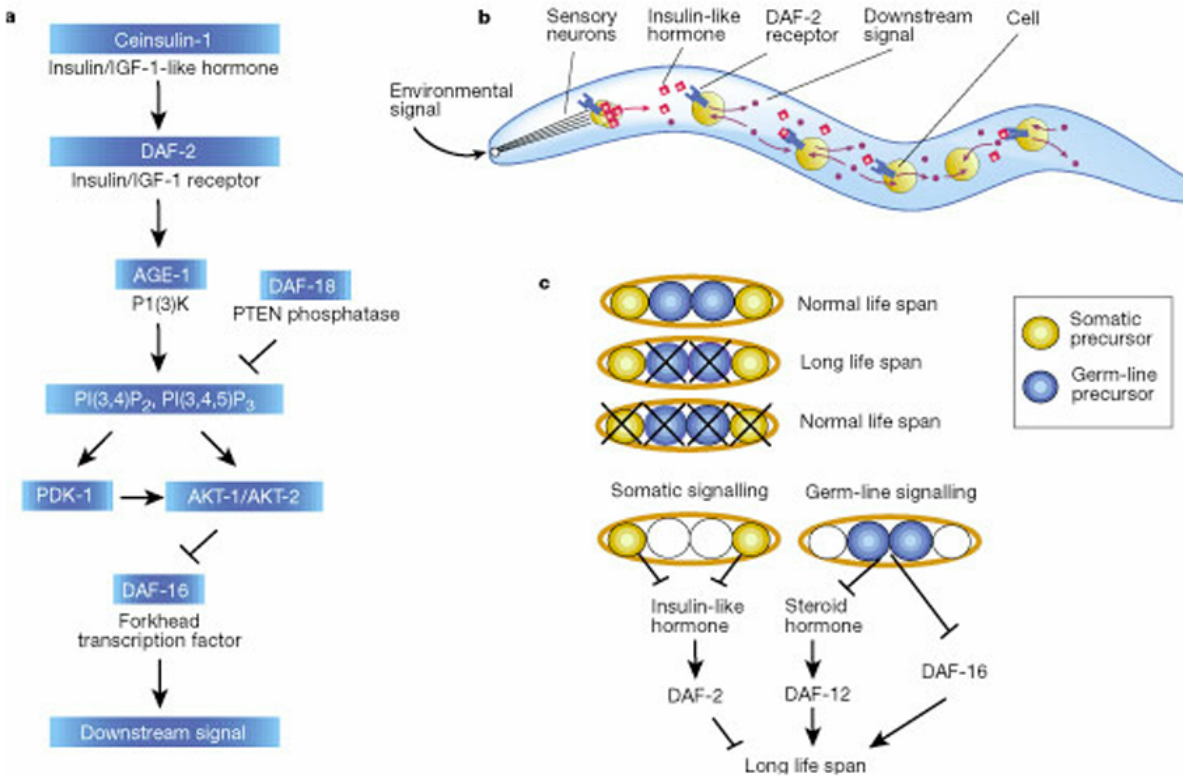
Cell Signaling



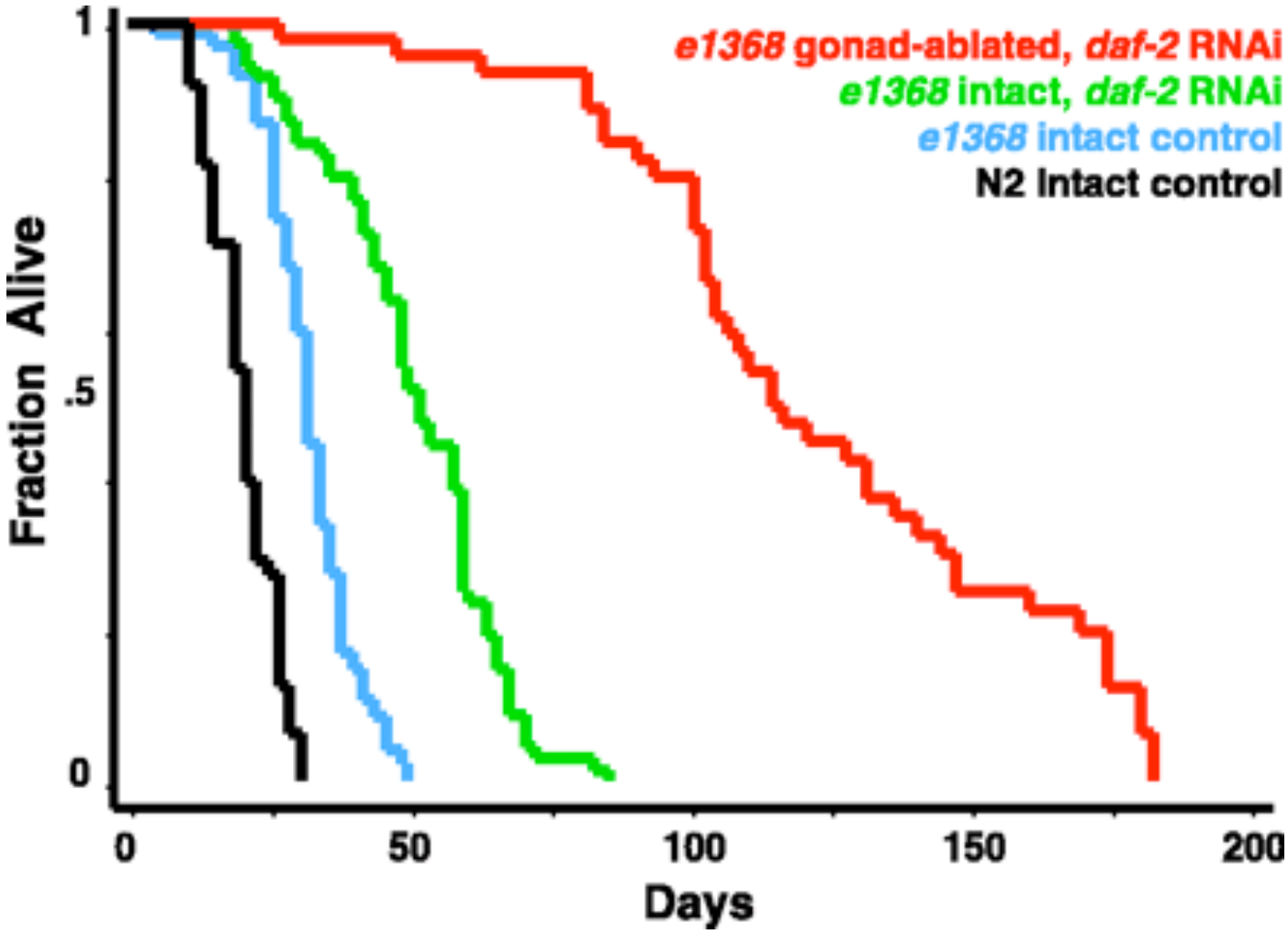
Insulin-like signaling pathway and aging

nature insight: review article

Close this window to return to the previous window



daf-2 (IL receptor) mutants live longer



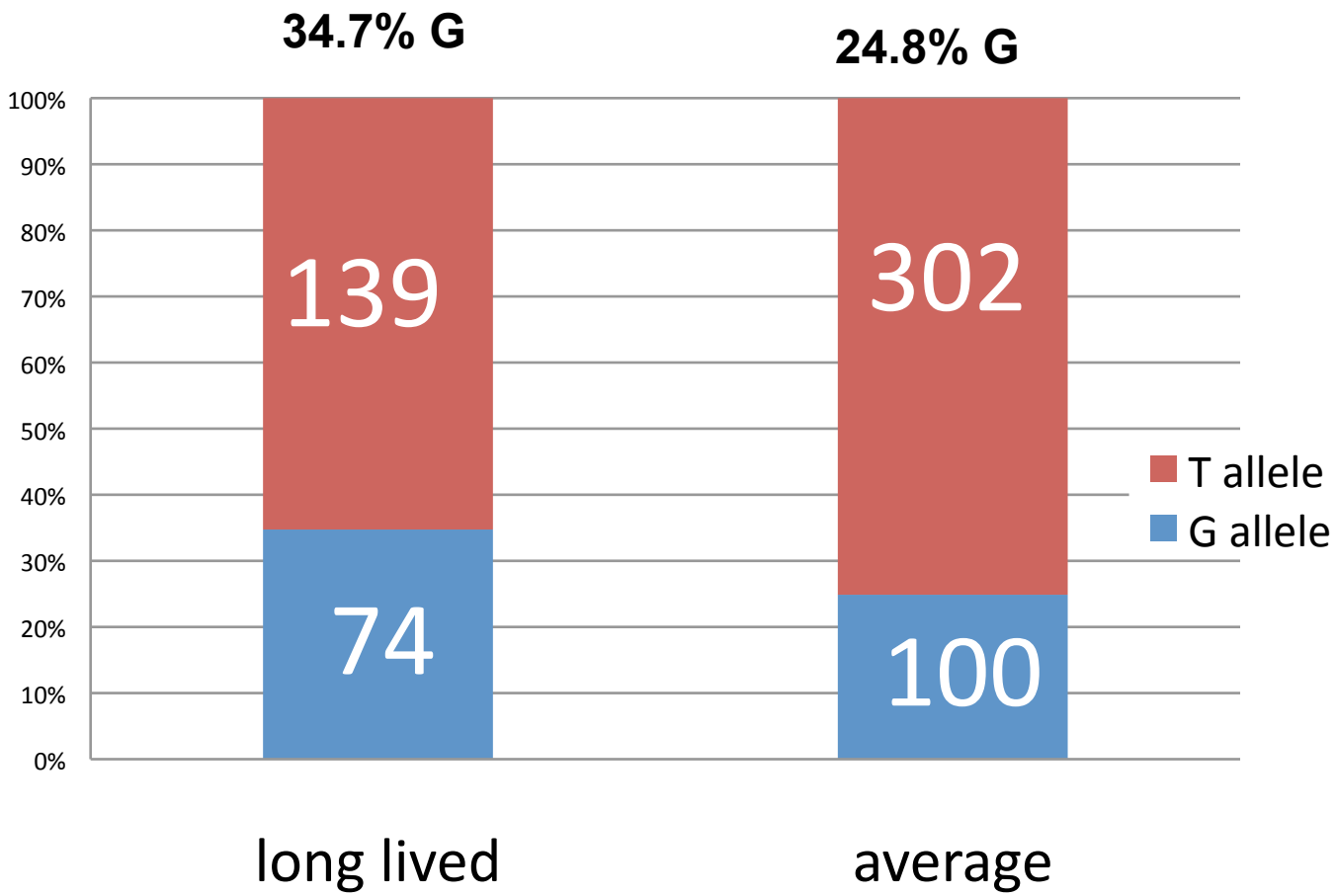
FOXOA3

Willcox et al., PNAS, 2008

- Start with healthy male Japanese in 1991
- 402 died before age 81 = average life Japanese
- 213 lived to 2007 = old Japanese
- Look at genotype of FOXO3A to see if there is a difference

FOXO3A Longevity

P = .0002



FOXO3A odds ratio

Table 3. FOXO3A3 genotype by case–control status

	FOXO 3A3 Genotype (rs 2802292)		
Case-Control Status	TT	TG	GG
Average-Lived Phenotype*	223 (55%)	153 (38%)	26 (6%)
Longevity Phenotype†	81 (38%)	106 (50%)	26 (12%)
p value for Pearson Exact test‡		0.000091	
p value after Bonferroni adjustment		0.00135	

*Number and percentage of subjects from $n = 402$ "average-lived" decreased controls (mean attained age 78.5 years).
†Number and percent of subjects from $n = 213$ "long-lived" cases (mean attained age 97.9 years).
‡From the exact Pearson χ^2 test comparing the genotype frequencies in the cases and controls.

Willcox et al

- For long-lived, GG/TT is 26/81 = .32
- For average-lived, GG/TT is 26/223 = .11
- Odds ratio is .32/.11 = 2.75

FOXO3A odds ratio

Table 3. FOXO3A3 genotype by case–control status

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‡From the exact Pearson χ^2 test comparing the genotype frequencies in the cases and controls.

- For long-lived, GT/TT is 106/81 = 1.30
- For average-lived, GT/TT is 153/223 = .686
- Odds ratio is 1.30/.686 = 1.89
- Stuart is GT (yay)

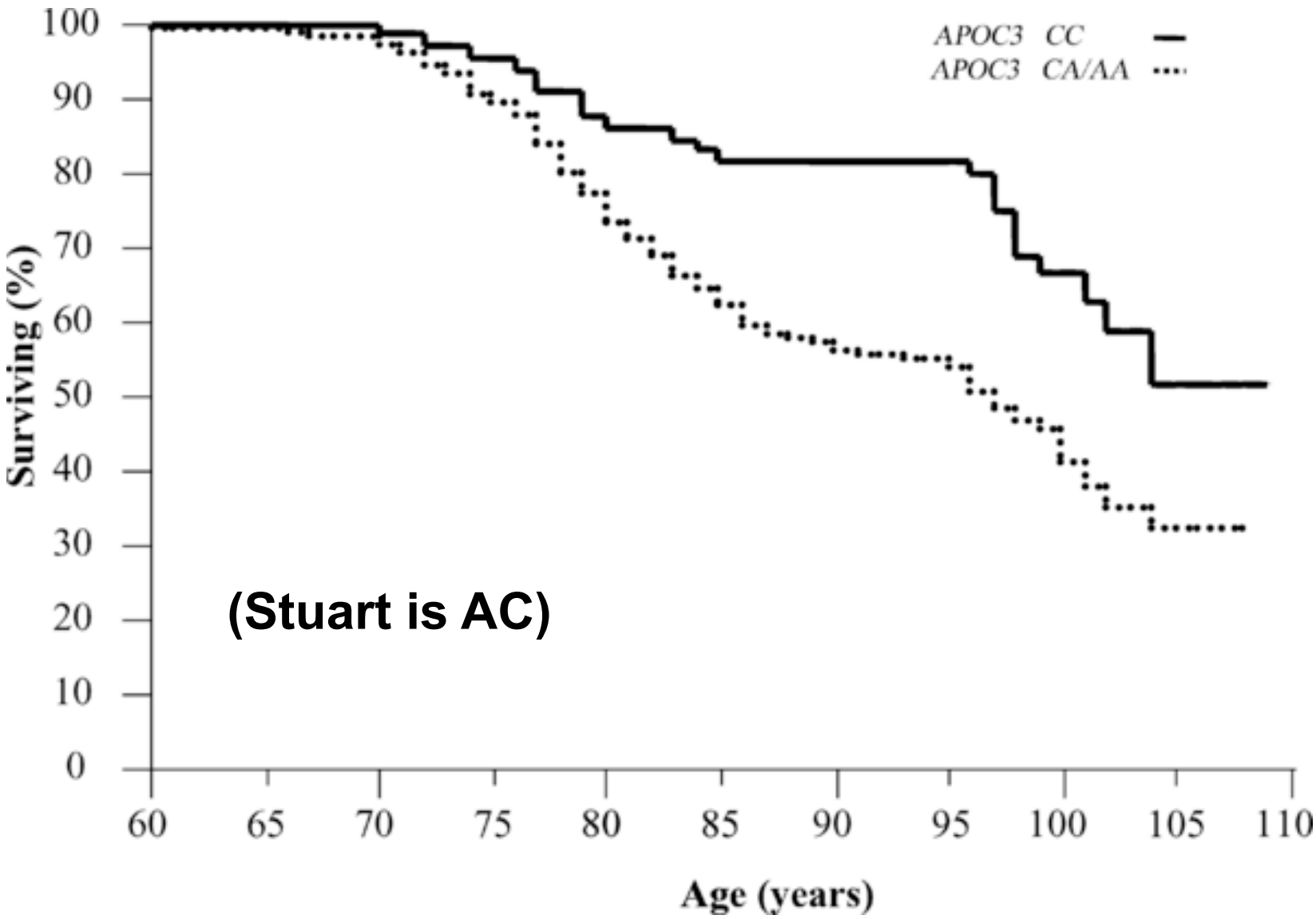
IGF1R

Suh et al., PNAS, 2008

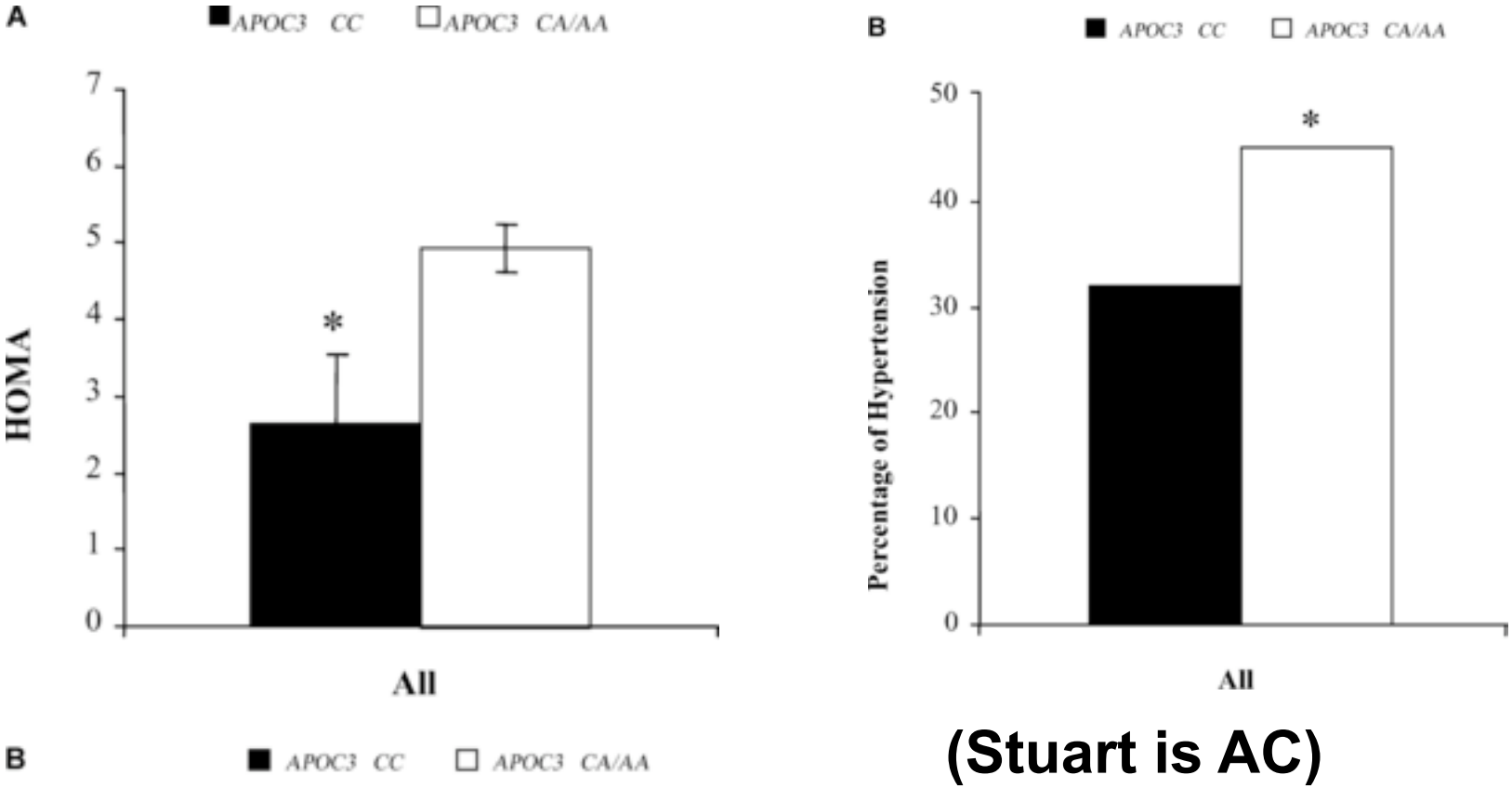
		Cent.	Non-Cent.
rs34516635	244G>A	2 het./384	0 het/312
	1355G>A	7 het./384	1 het/312

APOC3

- APOC3 is a major component of very low density lipoproteins and chylomicron remnants; it is also a minor component of HDL
- At rs2542052, the *C* allele is associated with lower expression compared to the *T* allele


APOC3 CC
APOC3 CA/AA
Surviving (%)
100
90
80
70
60
50
40
30
20
10
0
60
65
70
75
80
85
90
95
100
105
110
Age (years)
(Stuart is AC)

APOC3(CC) associates with better insulin sensitivity and lower hypertension



(Stuart is AC)

Sciencexpress Report

Genetic Signatures of Exceptional Longevity in Humans

Paola Sebastiani,[1]* Nadia Solovieff,[1] Annibale Puca,[2] Stephen W. Hartley,[1] Efthymia Melista,[3] Stacy Andersen,[4] Daniel A. Dworkis,[3] Jemma B. Wilk,[5] Richard H. Myers,[5] Martin H. Steinberg,[6] Monty Montano,[3] Clinton T. Baldwin,[6,7] Thomas T. Perls[4]*

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Healthy aging is thought to reflect the combined influence of environmental factors (lifestyle choices) and genetic factors. To explore the genetic contribution, we undertook a genome-wide association study of exceptional longevity (EL) in 1055 centenarians and 1267 controls. Using these data, we built a genetic model that includes 150 single nucleotide polymorphisms (SNPs) and found that it could predict EL with 77% accuracy in an independent set of centenarians and controls. Further in-silico analysis revealed that 90% of centenarians can be grouped into 19 clusters characterized by different combinations of SNP genotypes—or genetic signatures—of varying predictive value. The different signatures, which attest to the genetic complexity of EL, correlated with differences in the prevalence and age of onset of age-associated diseases (e.g., dementia, hypertension, and cardiovascular disease) and may help dissect this complex phenotype into subphenotypes of healthy aging.

The average human lifespan in developed countries now

Based upon the hypothesis that exceptionally old individuals are carriers of multiple genetic variants that influence human lifespan (*4*), we conducted a genome-wide association study (GWAS) of centenarians. Centenarians are a model of healthy aging, as the onset of disability in these individuals is generally delayed until they are well into their mid-nineties (*5*, *6*). We studied 801 unrelated subjects enrolled in the New England Centenarian Study (NECS) and 926 genetically matched controls. NECS subjects were Caucasians who were born between 1890 and 1910 and had an age range of 95 to 119 years (median age 103 years). Figure S1 in the Supporting Online Material (*7*) describes the age distribution. Approximately one-third of the NECS sample included centenarians with a first-degree relative also achieving EL, thus enhancing the sample's power (*8*). Controls included 243 NECS referent subjects who were spouses of centenarian offspring or children of parents who died at the mean age of 73 years, and genome-wide SNP data of 683 subjects selected from the Illumina control database.

Study: Genes May Predict Who Lives to 100

By ALICE PARK Thursday, Jul. 01, 2010

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How long you live has a lot to do with your environment and lifestyle, but exceptional longevity may have even more to do with your genes. For the first time, researchers have identified a genetic recipe that accurately predicts who may live to 100 and beyond.

Scientists led by Dr. Thomas Perls at the Boston University School of Medicine conducted a genetic analysis of more than 1,000 centenarians and their matched

The Little Flaw in the Longevity-Gene Study That Could Be a Big Problem

How a faulty DNA chip, lax editorial review, and a few skipped steps turned a good study into bad science.

by Mary Carmichael

July 07, 2010

Science

dna evidence • dna technology

Guinness World Records

Photos: A look at the oldest achievers.

VIEW GALLERY

Remember that *Science* study from last week linking a whole bunch of genes—including unexpectedly powerful ones—to extreme old age in centenarians? NEWSWEEK reported that a number of outside experts thought it sounded too good to be true, perhaps because of an error in the way the genes were identified that could cause false-positive results. Since last Thurday, they've been trying to figure out what might be lurking in the data, and now there's a suspect: a DNA chip called the 610-Quad, which is used to

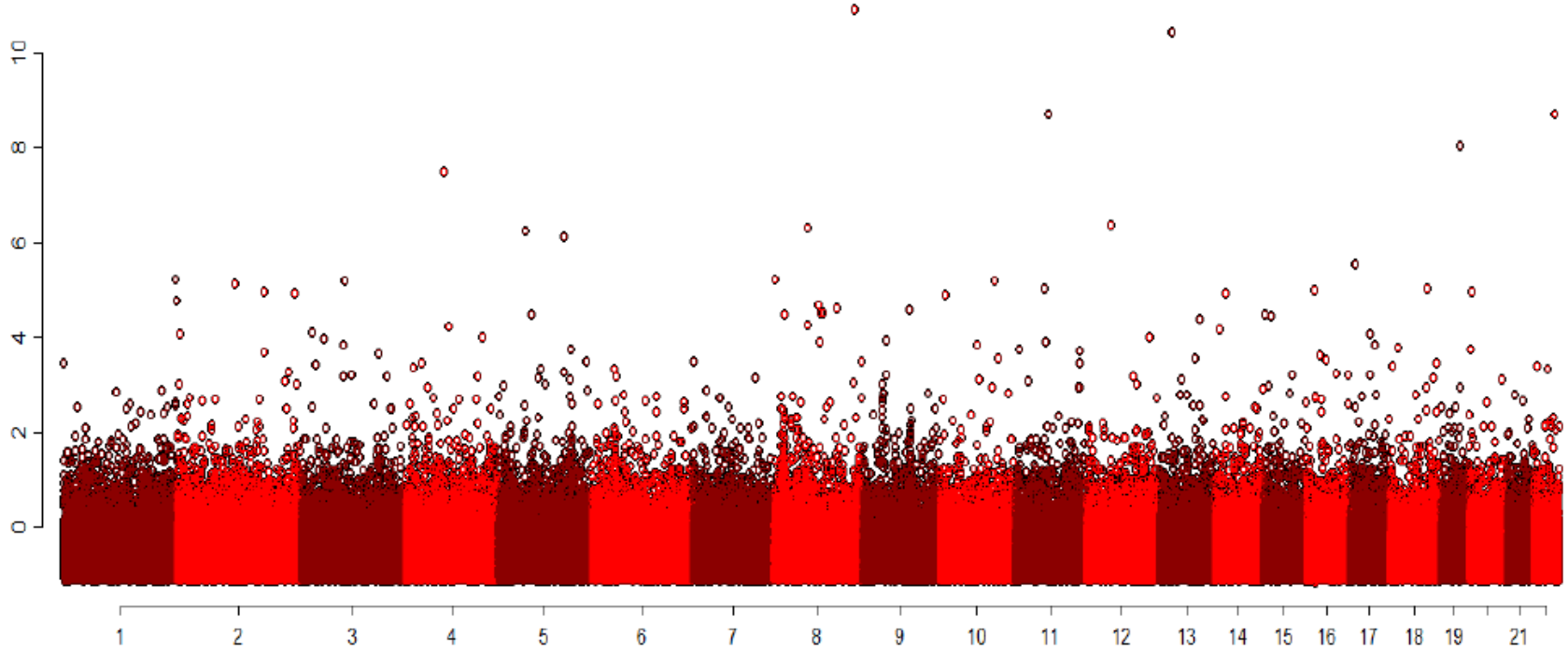
Trending on Newsweek

The Trouble With Using Undergrads for Research

'Sex at Dawn: The Prehistoric Origins of Modern Sexuality'

- 801 centenarians in group 1, 254 in group 2
- 926 controls
- 295,000 SNPs
- Found 33 SNPs associated with longevity

Fig. S5. The Manhattan plot displays the maximum log10(Bayes Factor) (y-axis) for each of the analyzed SNPs.



33 SNPs associated with extreme longevity

Table S1: Genome wide significant SNPs in the discovery, replication, and aggregated sets.

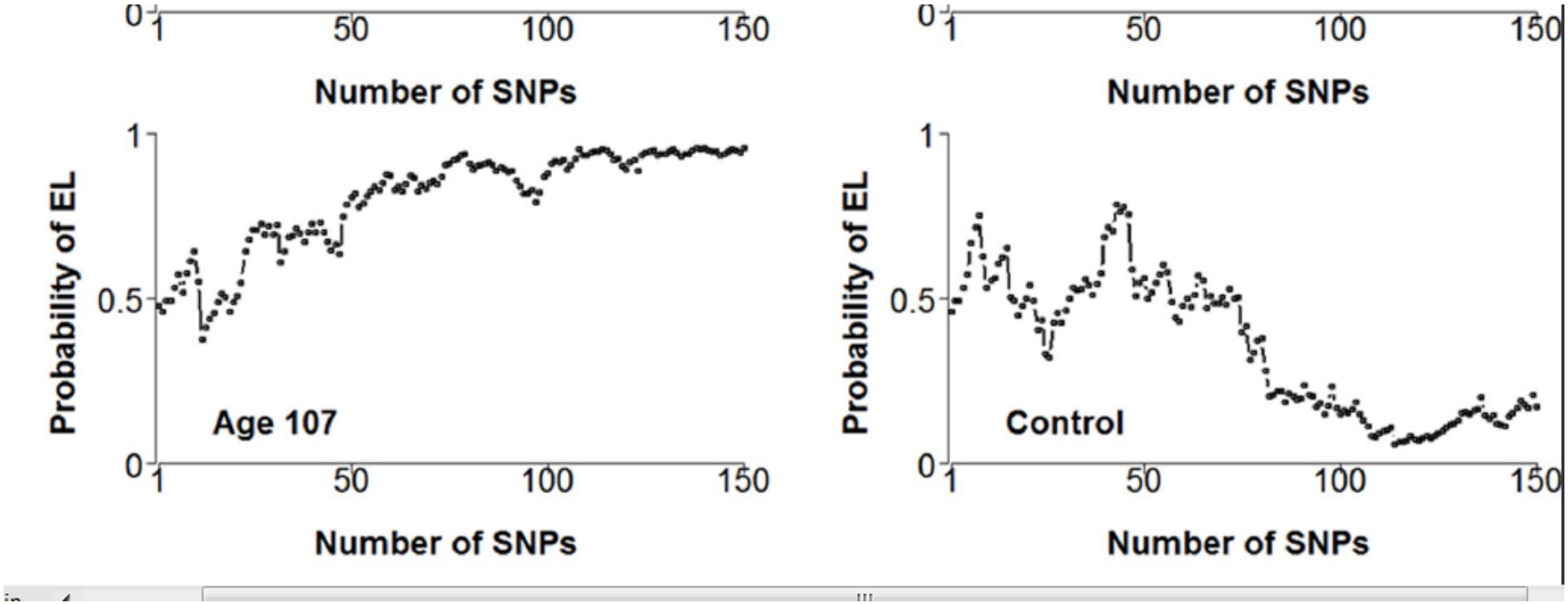
SNP	Gene	Chrom	Alleles	Discovery Set (801, 926)			
				LOG10(BF)	p-value	OR	p(A)
rs1036819	***ZFAT***	chr8:135681127	CC v AA/AC	10.92	2.89E-12	6.12	0.09/0.01
rs1455311		chr4:80183611	GG v AA/AG	7.48	2.11E-09	3.77	0.10/0.03
rs2075650	***TOMM40/APOE***	chr19:50087459	AG/GG v AA	6.39	8.81E-09	0.49	0.15/0.26
rs1436013		chr8:58940672	AC/CC v AA	6.31	8.69E-09	0.52	0.23/0.36
[illegible]	[illegible]	[illegible]	[illegible]	5.89	5.00E-08	2.31	0.91/0.81

Stuart = AA

Aging signature

- 254 centenarians, 926 control
- Calculate aging signature
- 77% of centenarians have good aging signature
- 23% of controls have good aging signature

Aging signature



Stuart's Aging Signature