

Exceptional longevity, cognitive decline and dementia

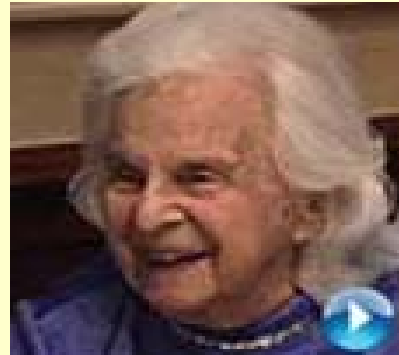
Amy E. Sanders, MD
Assistant Professor of Neurology

Albert Einstein College of Medicine of Yeshiva University,
Bronx, NY

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Why should longevity researchers consider cognitive aging and dementia?

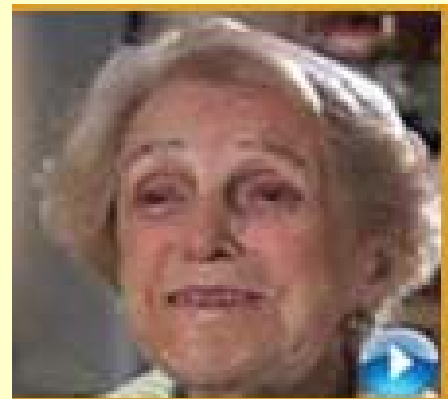
- Incidence of dementia increases exponentially with age after 65
- Dementia is a leading cause of death in the elderly
- Long life is most valuable if cognitive function is preserved.....



Age 103



Age 98



Age 96

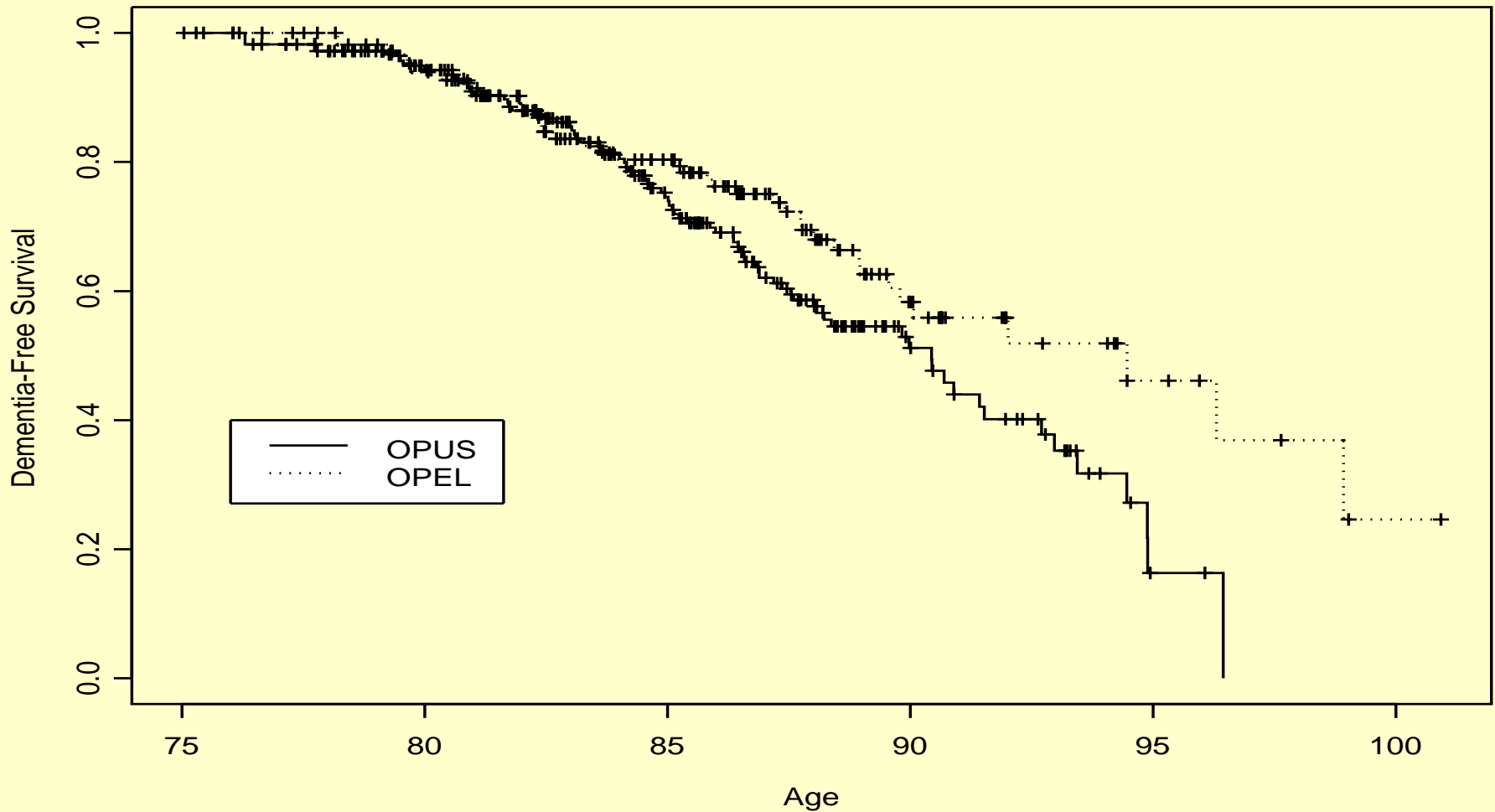
Offspring of parents with exceptional longevity (OPEL) in the Bronx Aging Study

- *Bronx Aging Study*: From 1981-83 we enrolled 488 community-residing 75-85 year olds (born between 1896 and 1908)
- 424 participants followed to dementia (n=113) or death
- Parents of BAS subjects were born prior to 1880 on average
- Defined OPEL as having at least one parent reaching the age of 85 (n=149)



- OPEL had lower lifetime risk of any dementia than OPUS
 - HR 0.64 (95% CI 0.43-0.97)
 - Compared to OPUS, OPEL 36% less likely to develop any dementia

Survival Plot for dementia in OPUS vs OPEL



OPEL have a reduced risk of AD and less memory decline

- OPEL had lower lifetime risk of AD than OPUS
 - HR 0.61 (95% CI 0.37-0.99)
 - adjusted for sex, education, race/ethnicity, and self-reported history of hypertension, MI, diabetes and stroke
- In OPEL, episodic memory declined 30% more slowly as a function of age than in OPUS (p=0.03)

Why are OPELs protected against cognitive decline and AD?

- OPEL may have healthier life styles

Or.....

- OPEL may carry protective “longevity genes”
 - Increase cognitive reserve (ability to withstand pathology) ?
 - Protect against vascular disease ?
 - Protect against AD pathology ?

unknown

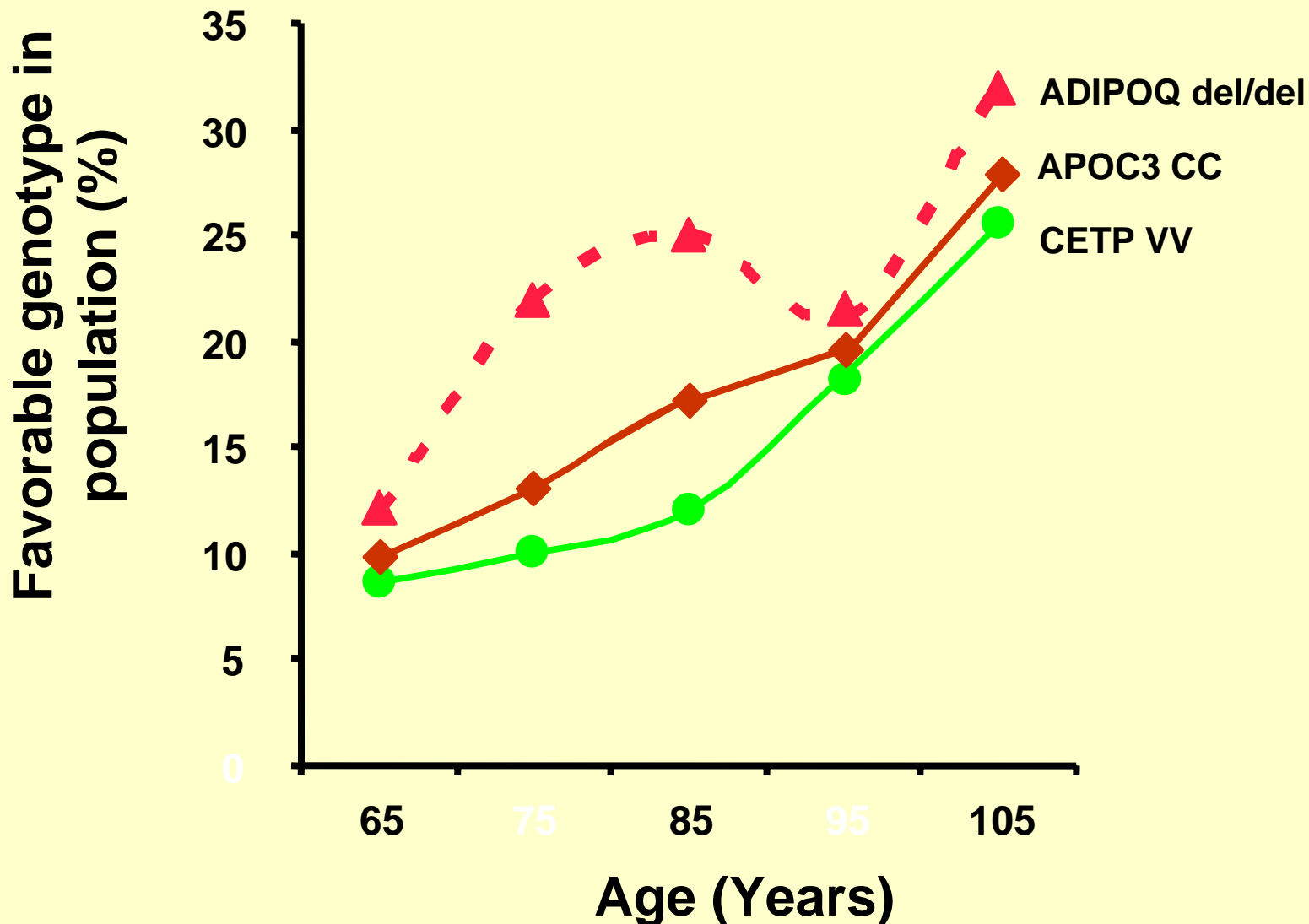
Genes and Alzheimer's disease

- Alzheimer's disease is a complex disorder
- Majority of cases are non-familial (late onset)
 - *APOE*
 - Clinical studies suggest 50-60% $\epsilon 4$ positive
 - Emerging candidate genes and genes from GWAS
- Familial AD (onset < 60 yrs; <5%)
 - All known AD genes are related to β -amyloid
 - Presenilin I, II (chr 14, 1)
 - Amyloid Precursor Protein (chr 21)

Do longevity genes protect against cognitive decline and AD?

- LonGenity PPG: focuses on OPEL and OPUS in an Ashkenazi Jewish founder population
- Compares gene frequency in Centenarians, their offspring and age mates of their offspring
- Hypothesis: Longevity gene frequency
Centenarians > Offspring > Controls
- Longevity genes protect against cognitive aging and possibly AD

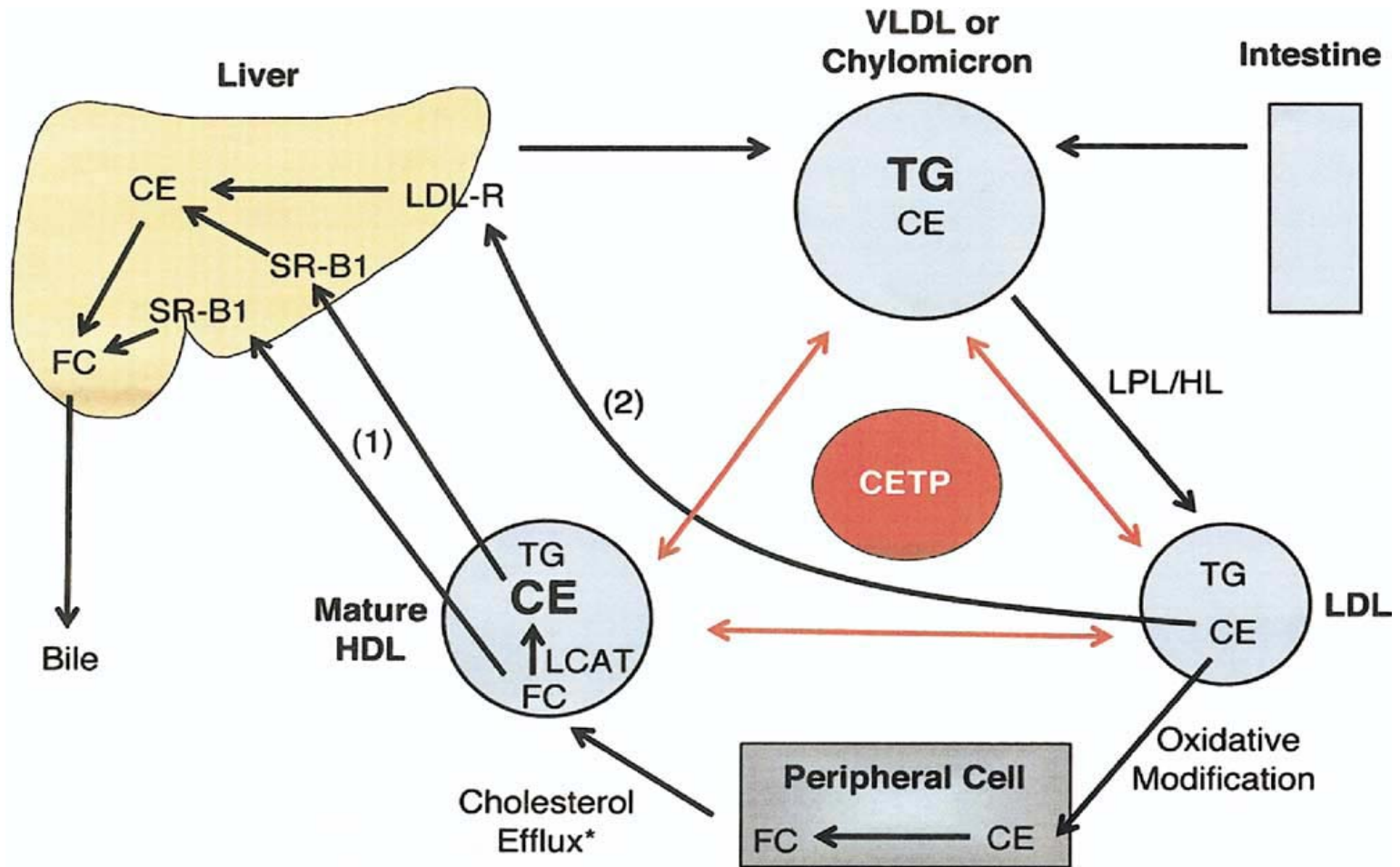
Favorable Longevity-Associated Genotypes in Unrelated 65-108 Year-Old Ashkenazi Individuals



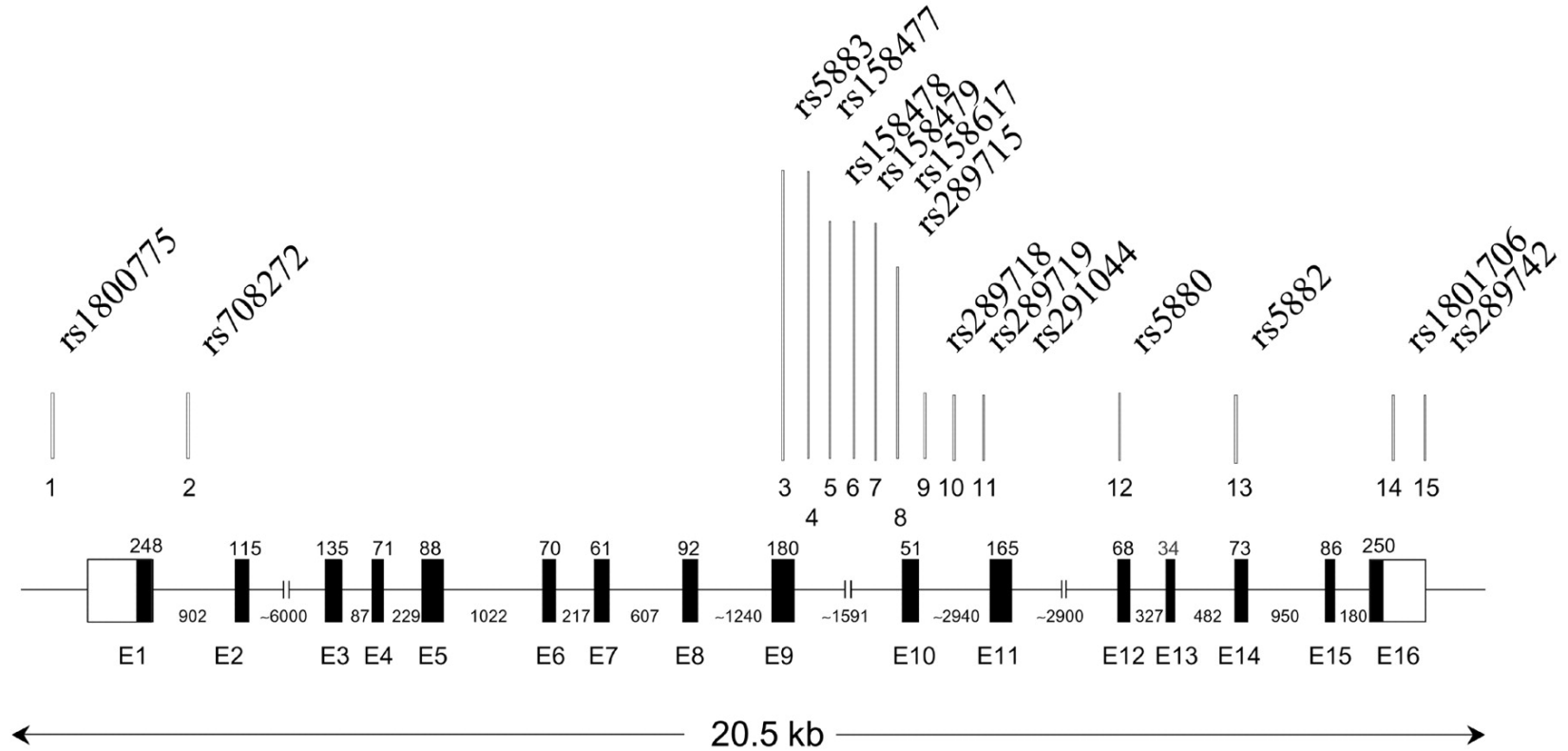
CETP

- Chromosome 16q21
- 16 exons
- Codon 405 located in exon 14
- Hydrophobic plasma glycoprotein

CETP in Plasma Lipid Transport



Structure of the CETP gene



Is *CETP* a “longevity gene”?

- Phenotype in Ashkenazi Jewish centenarians and their offspring
 - increased lipoprotein particle size (HDL and LDL)
 - lower prevalence of hypertension, cardiovascular disease, and the metabolic syndrome
 - associated with increased cross-sectional frequency of V-allele homozygosity at rs5882: 24.8% of centenarians compared to 8.6% of unrelated controls

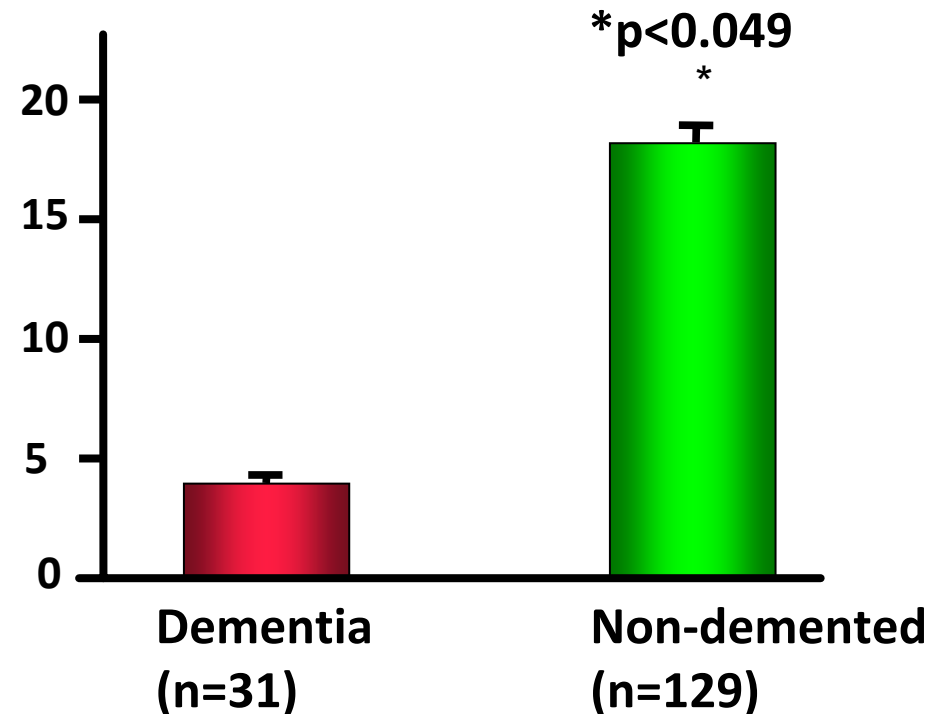
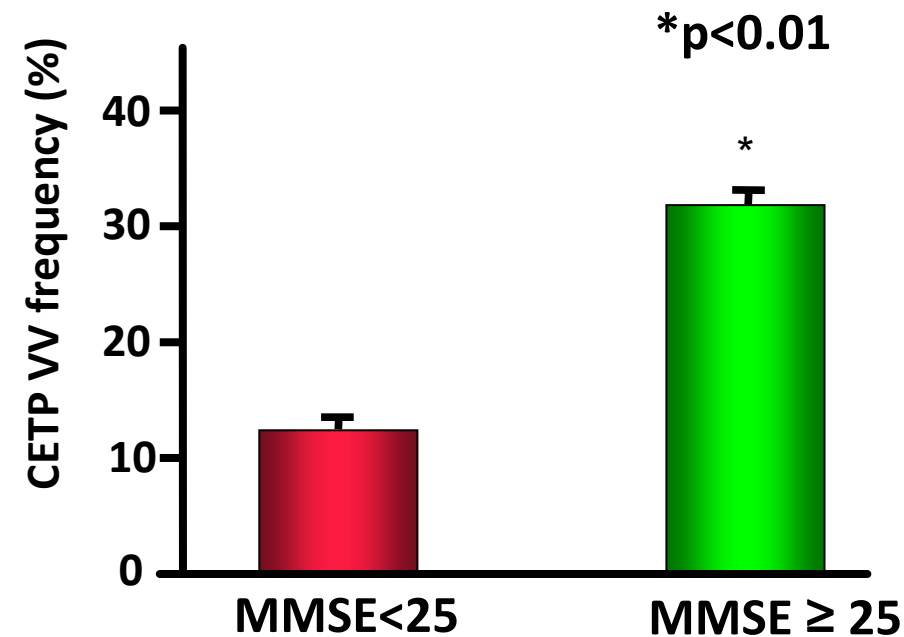
More on.....Why *CETP* ?

- *CETP* may be associated with reduced cardiovascular disease risk and healthy aging
 - In Framingham Offspring Study, OR for prevalent CHD associated with B2 allele of TaqIB polymorphism 0.73 in men
 - In Honolulu Heart Study, elderly Japanese men with Int14A variant showed trend for lower mortality along with significantly higher HDL-C and increased likelihood of “healthy survival”

CETP VV genotype: cognitive function, and dementia

Centenarians

Einstein Aging Study



Why *CETP* and Dementia?

- Genetic association studies examining *CETP* and dementia risk are inconclusive
 - Nine papers listed at *Alzgene* website
 - Numerous polymorphisms investigated
 - Six negative, two positive, one marginal
 - All used case-control study designs
 - Eight of nine used clinic-based populations

Study Aim

To investigate associations between incident dementia risk and *CETP* genotype in a community-based sample of healthy older adults without dementia at baseline.

-codon 405, single-nucleotide polymorphism

-isoleucine → valine; I405V *aka* V405

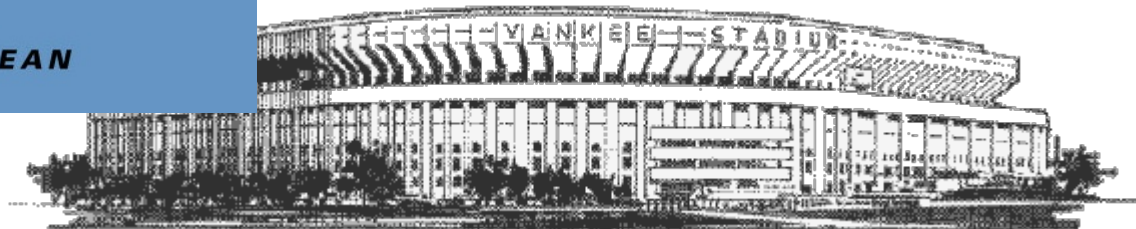
-NCBI dbSNP rs 5882)

Study Hypothesis

The V allele will be associated with lower risk of dementia and Alzheimer's disease

- codon 405, single-nucleotide polymorphism
- isoleucine → valine; I405V *aka* V405
- NCBI dbSNP rs 5882

Einstein Aging Study, Bronx NY



Einstein Aging Study

- Longitudinal study of aging and cognition
- Systematic random sampling methods
- Since 1993, > 1900 individuals older than age 70, primarily English-speaking and Caucasian
- Non-demented at study entry

Einstein Aging Study

- Annual clinical visits:
 - Medical history (10-item scale)
 - Functional assessment (LB), GDS
 - Neurological examination
 - Neuropsychological testing
 - Fasting blood sample
 - Consensus dementia diagnosis using DSM-IV for dementia; NINCDS/ADRDA for Alzheimer's disease

Analysis Population

- *CETP* genotype available on 608 individuals
- Exclusions: prevalent dementia, < 2 visits
- 523 individuals in the analysis
- Mean age at baseline 78
- 61% female; 26% African American
- Mean education 14 years
- Mean follow-up time 4.3 years

Statistical Methods

- Cox Proportional Hazards Models
 - Age as time scale
 - Estimation of relative dementia risk in V405 homozygotes and heterozygotes
- Three nested models progressively adjusted for
 - Demographics (sex, education, race)
 - Medical co-morbidities (10-item scale)
 - Presence of *APOE* $\epsilon 4$ allele

Results

- Relatively healthy: median 1.0 medical problems endorsed
- No functional decline: median score 7 out of 8 on Lawton-Brody scale
- Few depressive symptoms: median GDS 2
- Race: higher prevalence of VV in African Americans than whites
- premorbid intelligence (homozygotes worse)

Results

- Allele frequency for valine 43.5%
- Genotype frequency:
 - V-V: 21% (n = 110)
 - I-V: 45% (n = 235)
 - I-I: 34% (n = 178)
- Genotype frequencies differed slightly from Hardy-Weinberg equilibrium ($p=0.05$)
- 40 incident dementia cases (35 AD)

CETP V405 Genotype and Risk for Dementia and Alzheimer Disease

Table 4. CETP V405 Genotype and Risk for Dementia and Alzheimer Disease^a

Category	Model 1 ^b		Model 2 ^c		Model 3 ^d	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Risk for dementia vs isoleucine homozygotes						
Valine heterozygotes (n = 16)	0.52 (0.26-1.06)	.07	0.53 (0.26-1.09)	.08	0.57 (0.28-1.15)	.12
Valine homozygotes (n = 5)	0.29 (0.10-0.85)	.02	0.28 (0.09-0.84)	.02	0.28 (0.10-0.85)	.02
Risk for Alzheimer disease vs isoleucine homozygotes						
Valine heterozygotes (n = 14)	0.52 (0.24-1.13)	.10	0.53 (0.25-1.2)	.11	0.56 (0.26-1.2)	.14
Valine homozygotes (n = 5)	0.31 (0.10-0.96)	.04	0.30 (0.10-0.94)	.04	0.31 (0.10-0.95)	.04

Abbreviations: CI, confidence interval; HR, hazard ratio.

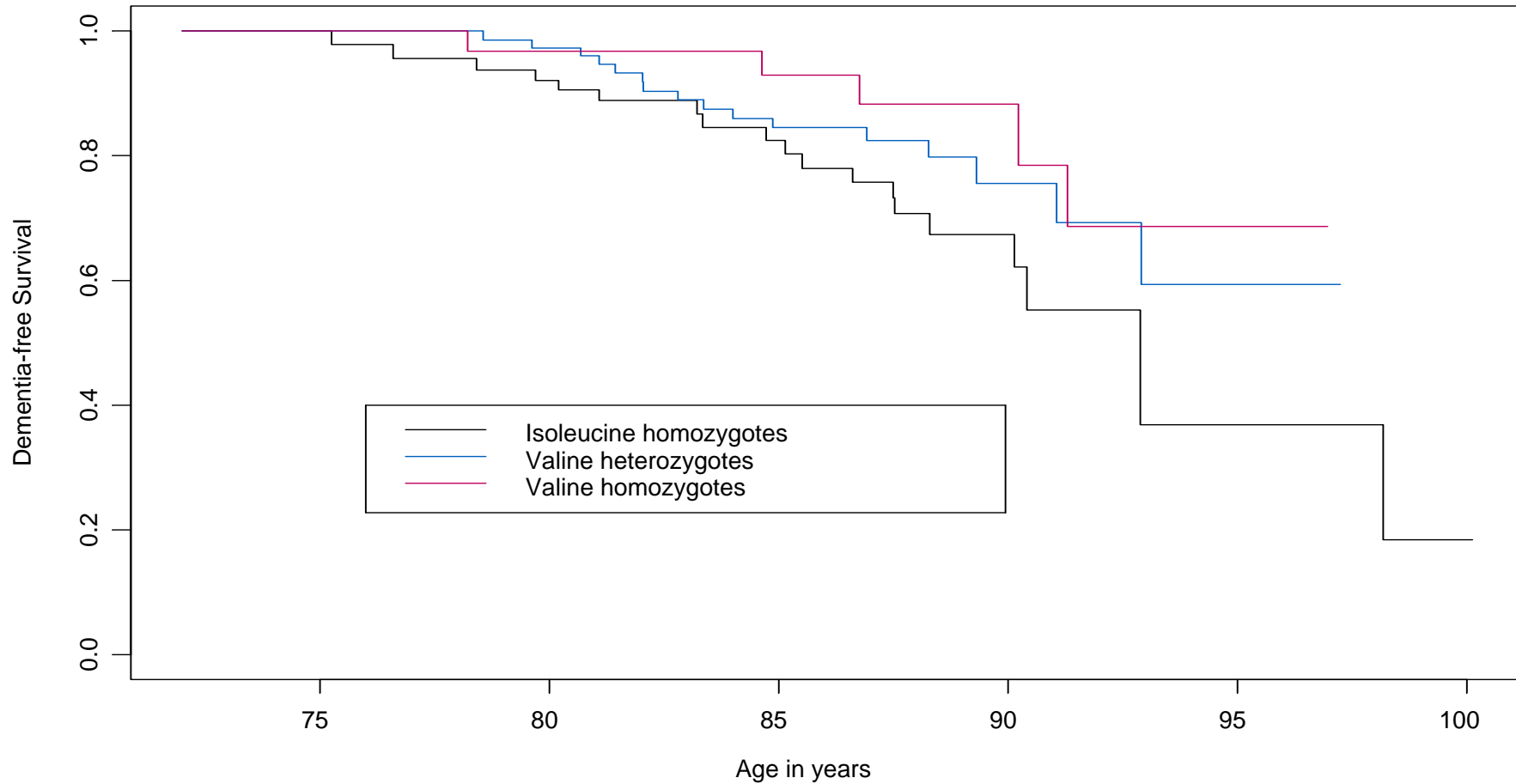
^aP values from Cox proportional hazard models with delayed entry and age as the time scale. There were 40 incident cases of dementia (19 in the reference group) and 35 incident cases of Alzheimer disease (16 in the reference group).

^bAdjusted for sex, years of education, non-Ashkenazi white race, and black race.

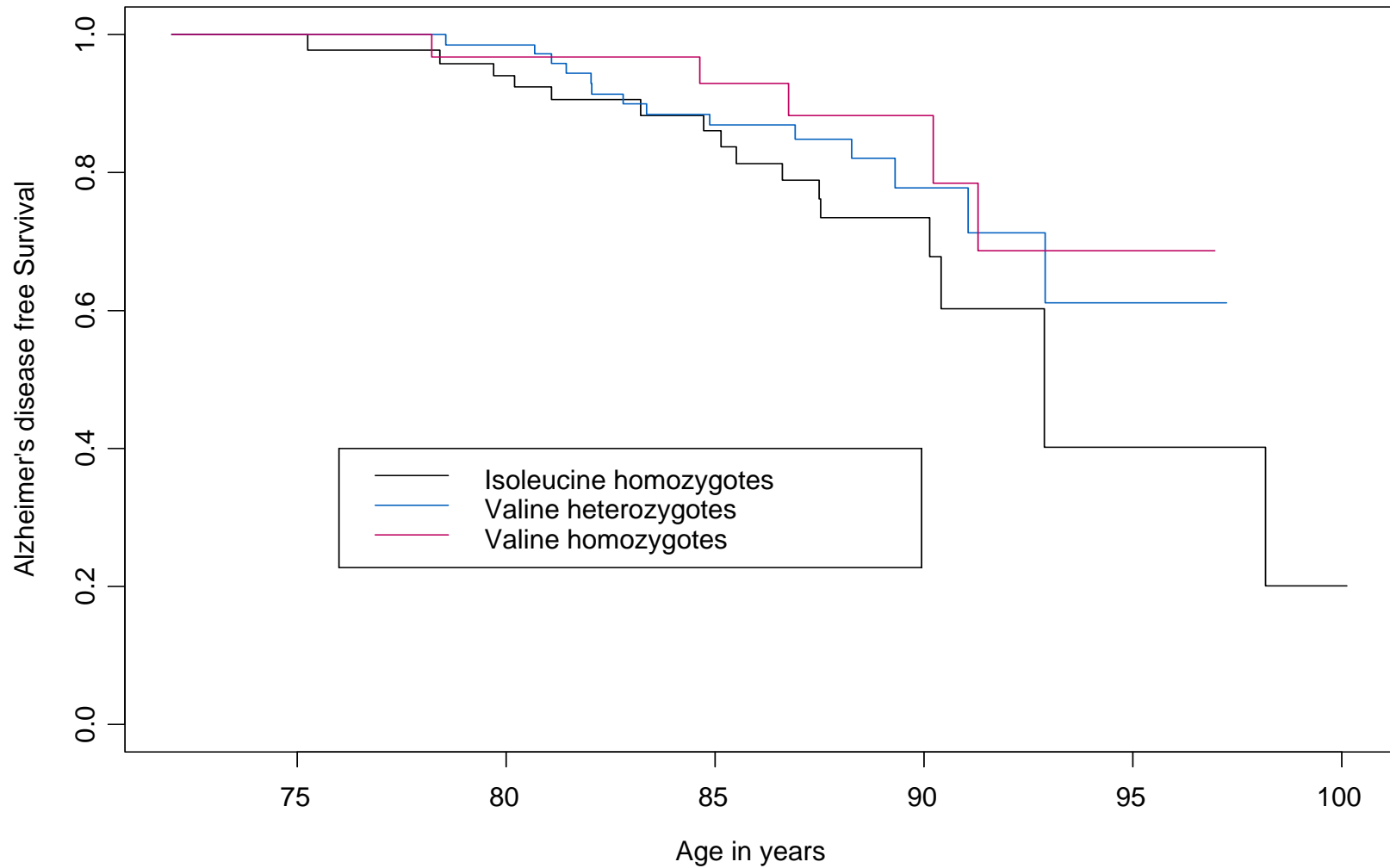
^cAdjusted for the covariates in model 1 plus an additional adjustment for medical comorbidities as measured by the Medical Comorbidity Index.

^dAdjusted for the covariates in model 2 plus an additional adjustment for presence of an apolipoprotein E ε4 allele.

Dementia-Free survival



Alzheimer's-free survival



Summary and Implications

- Presence of V-allele at codon 405 in the *CETP* gene was associated with reduced incidence of both all-cause dementia and Alzheimer's disease
- Since *CETP* has also been associated with longevity, we hypothesize that in case-control studies protective effects may be attenuated by prolonged survival in cases having the beneficial allele

Limitations

- Sample size precluded analysis of dementia subtypes other than AD
- Community-residing relatively healthy population
- Diagnostic misclassification possible
- Selective attrition possible

Acknowledgements

Funding:

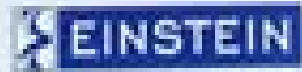
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- Einstein Aging Study participants and staff
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Einstein Aging Study



Albert Einstein College of Medicine
Yeshiva University

Science at the heart of medicine



The image features a classic hypnotic spiral background, consisting of concentric circles that create a sense of depth and motion. The color palette is primarily red and black, with the spiral transitioning from a dark red at the center to a black outer edge. Overlaid on this background is the iconic phrase "That's all Folks!" written in a white, elegant cursive script. The text is positioned diagonally across the center of the spiral, with the word "Folks!" being significantly larger and more prominent than "That's all".

That's all Folks!