

*“Does molecular biology tell
us anything about cognitive
function in older adults?”*

***MICRA Meeting
January 2011***



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Why study cognitive genetics?

Historically and Ethically controversial

Nature or Nurture?

Heritability

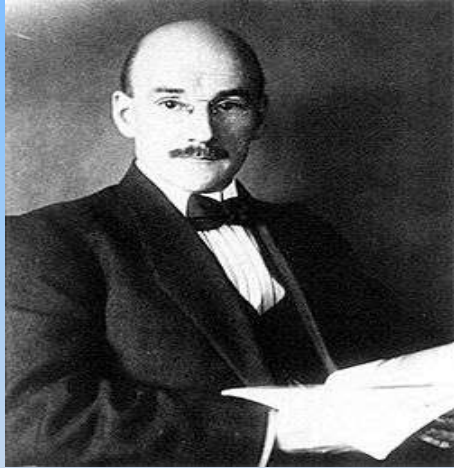
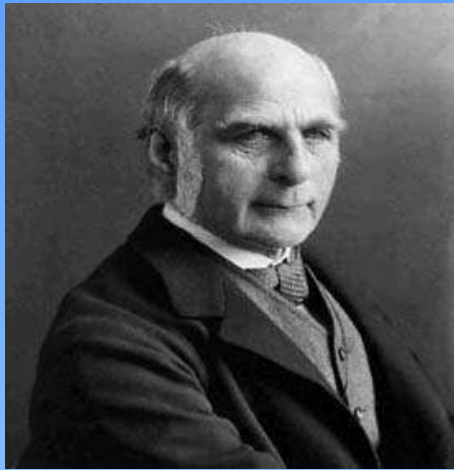
Environmental Influence

Manchester-Edinburgh BBSRC GWAS

Findings thus far

Future plans





A Controversial Past

1883 - Francis Galton

“supplanting inefficient human stock by better strains, by such efforts as may be reasonable, to further the ends of evolution more rapidly”

Galton F. (1883). *Inquires into human faculty*. Macmillan. London

1900 - Henry Goddard

IQ test rankings: “idiots, imbeciles, and morons”

1912 - Tests used at Ellis Island

Discovered that large percentages of the new immigrants are “feeble-minded”.

A Controversial Future?

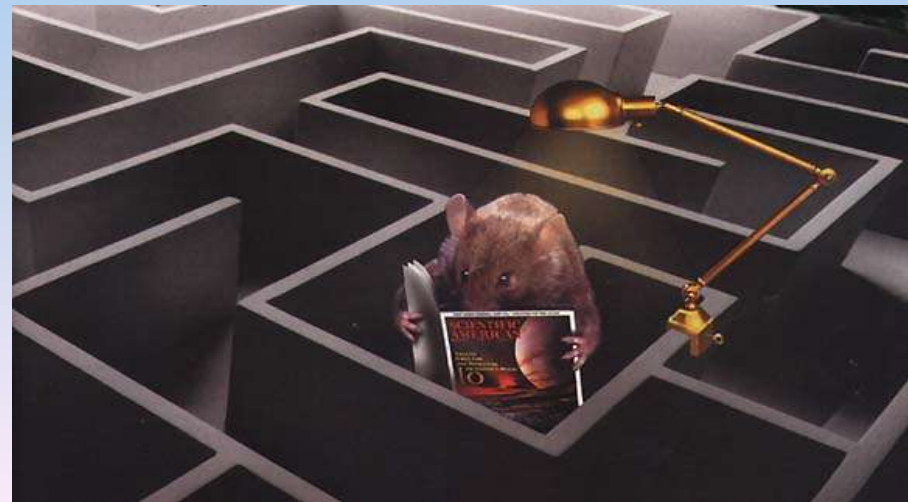
Ethical to develop “super-human” intellect?

How would it effect our personal identity?

Will we still value something we haven't worked for?

Will only the very rich have access to new drugs?

Should we screen embryo's to select for intelligence?



An Ageing Society

Average life expectancy ↑

5 hours/day past 200 yrs

In UK:

more people > 60 yrs than < 16 yrs
by 2050 1/3 UK population will be
> 60 yrs old

Cognitive impairment:

38% of all disabilities

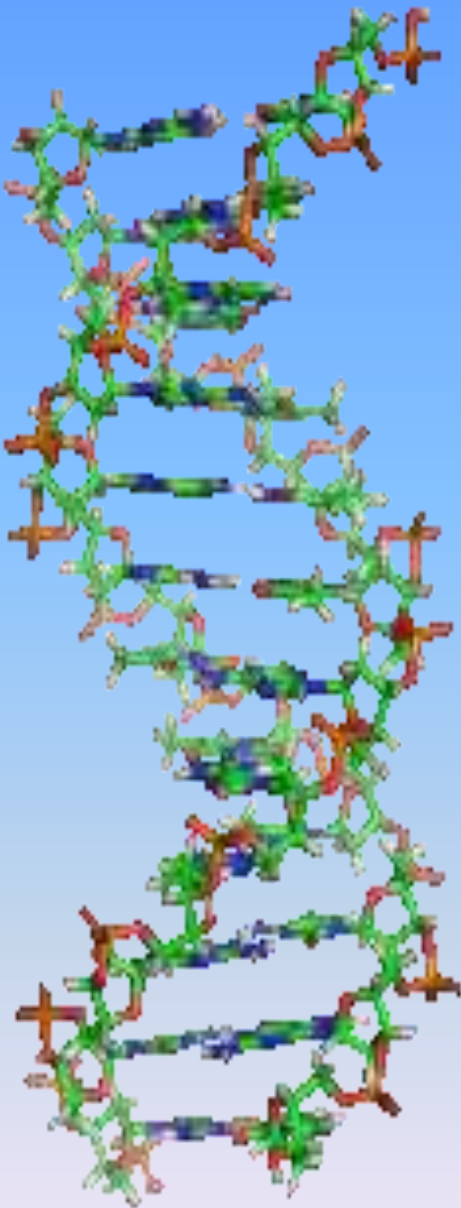
Costs Triple > £16.7 billion 2031

Most feared aspect of ageing



**"I don't feel old. I don't feel
anything until noon. Then
it's time for my nap."**

Bob Hope



Heritability of Intelligence

Level of cognitive ability

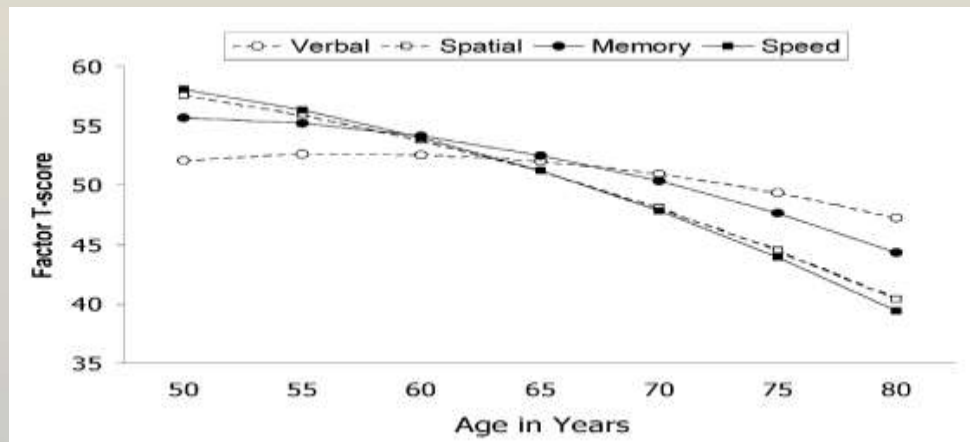
> 110, 000 twin/sib pairs: 50%

Bouchard and McGue, 2003

Rate of cognitive decline

778 aged >50 years, 13 yr: 30%

Finkel et al. 2005





Genes do not function independently!

BDNF and REST ($n=746$) association with cognition

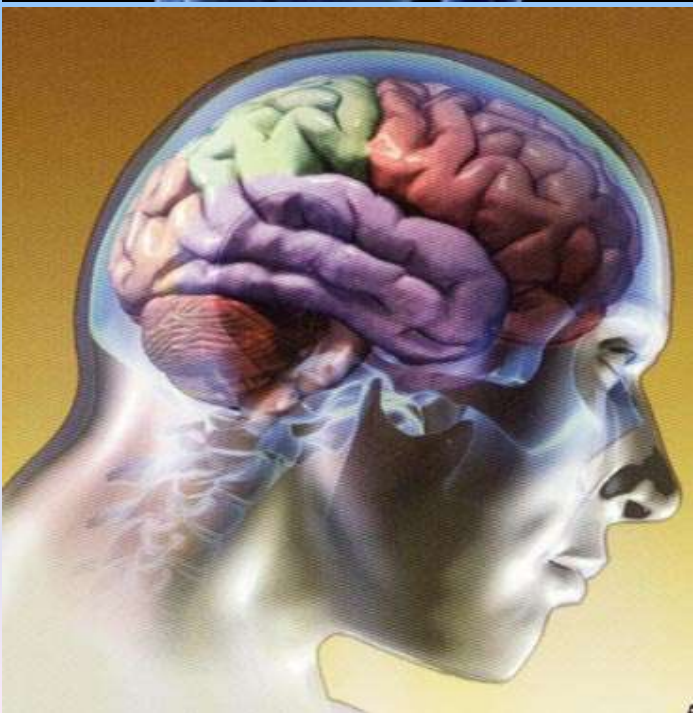
Miyajima et al, 2008

FADS2 and breast feeding ($n=3269$) association with IQ

Caspi et al, 2007

HFE and Lead ($n=358$) association with cognitive decline

Wang et al, 2008



Cognitive genetic association Studies 1995-2011

> 200 published reports (>50 genes)
population sizes ~300,
effect sizes: 0.1-21% (1%)

Neurotransmitter

BDNF, CHRM2, COMT, DBH, DRD2

Neurological diseases

APOE, CTSD, DISC1, DTNBP1

Development

ERBB4, MSX1, S100B

Metabolic

MTHFR, PPARG, PRNP, KL

Inflammation

HLA-DRB1, IL1B, TNFA



Conflicting Reports

Inadequate sample size

Population stratification

Variety of psychometric tests

Multiple testing

Lack of replication cohort

Longitudinal cohorts

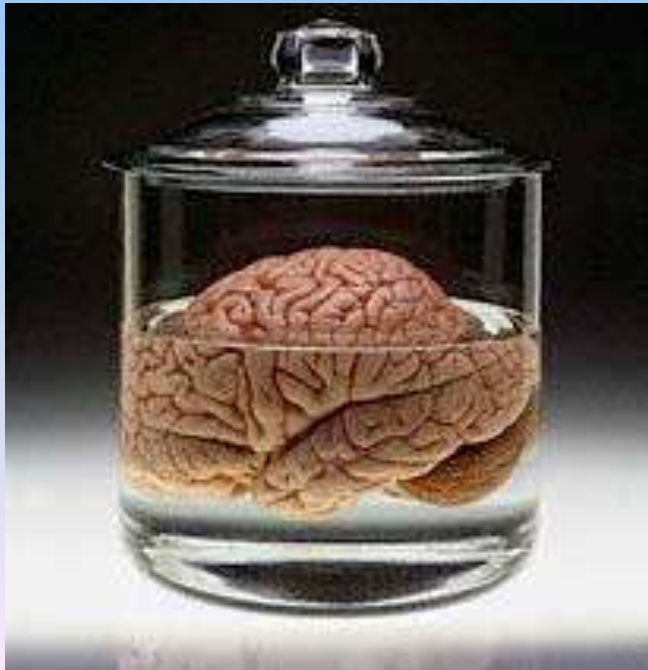
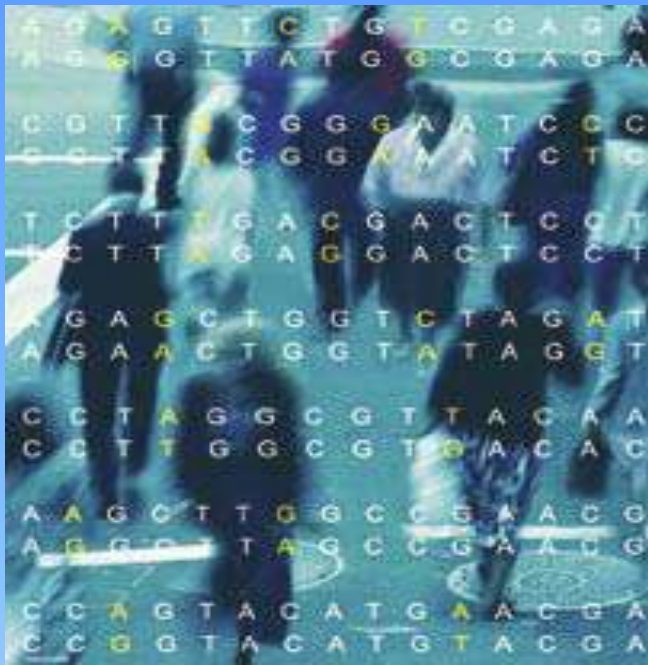
Practice effects

Selective drop-out

Inadequate follow-up

No consistent ^{published} replication

Payton A. Neuropsychol Rev. 2009. 19(4):451-77



MANCHESTER
1824

The University
of Manchester

University of Manchester Dyne Steele DNA bank

Volunteers recruited in 1983

Elderly 50 yrs+

Manchester and Newcastle

Tested every five years

Follow-up of up to 20 yrs

~1850 DNA samples

Phenotypes

Cognitive tests, physiological,
psychological, general health,
demographics, MRI, brain bank,
screened for dementia



University of Edinburgh Lothian Birth Cohorts 1921 and 1936

1st June 1932, 87,498 11 yr olds

4th June 1947, 70, 805 11 yr olds
Moray House IQ Test (45 min)

~2000 people: Lothian (Edinburgh)
and Aberdeen underwent
psychometric testing
Memory: working, spatial, verbal
processing speed, executive functioning
and Moray House Test
and DNA collection

THE SCOTTISH COUNCIL FOR
RESEARCH IN EDUCATION

1932 MENTAL SURVEY TEST

SUITABLE FOR PUPILS OF
TEN AND ELEVEN YEARS OF AGE

MENTAL SURVEY TEST, 8 pp., 4d.
PRELIMINARY PRACTICE TEST, 2 pp., 1d.
INSTRUCTIONS FOR ADMINISTRATION,
8 pp., 4d.

SPECIMEN SET - 9d., post free

UNIVERSITY OF LONDON PRESS LTD.

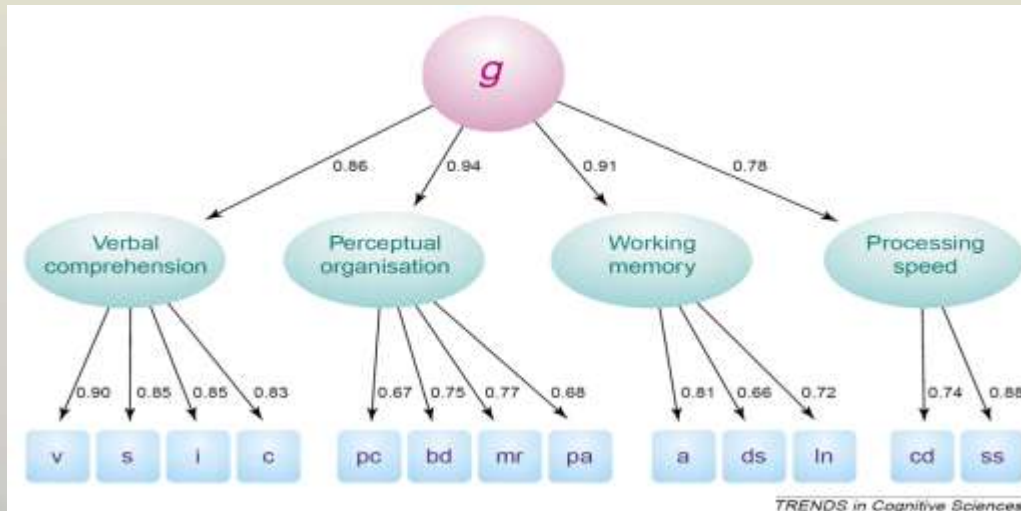
WAR-TIME ADDRESS:
ST HUGH'S SCHOOL, BICKLEY, KENT



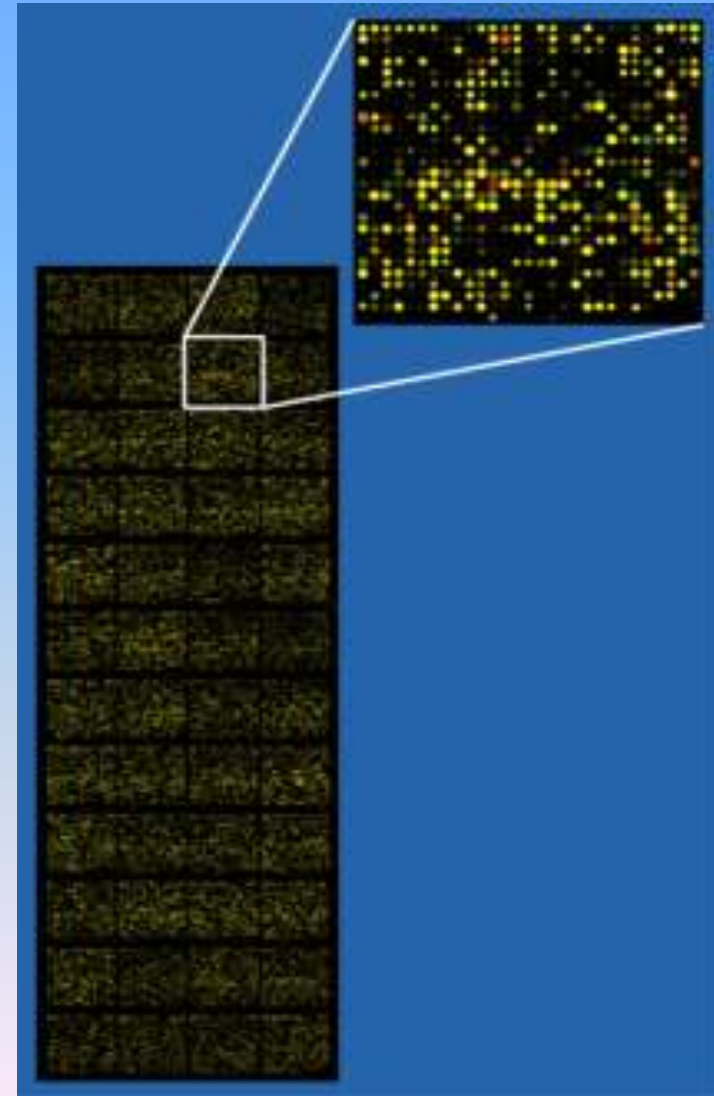
Manchester-Edinburgh Collaboration

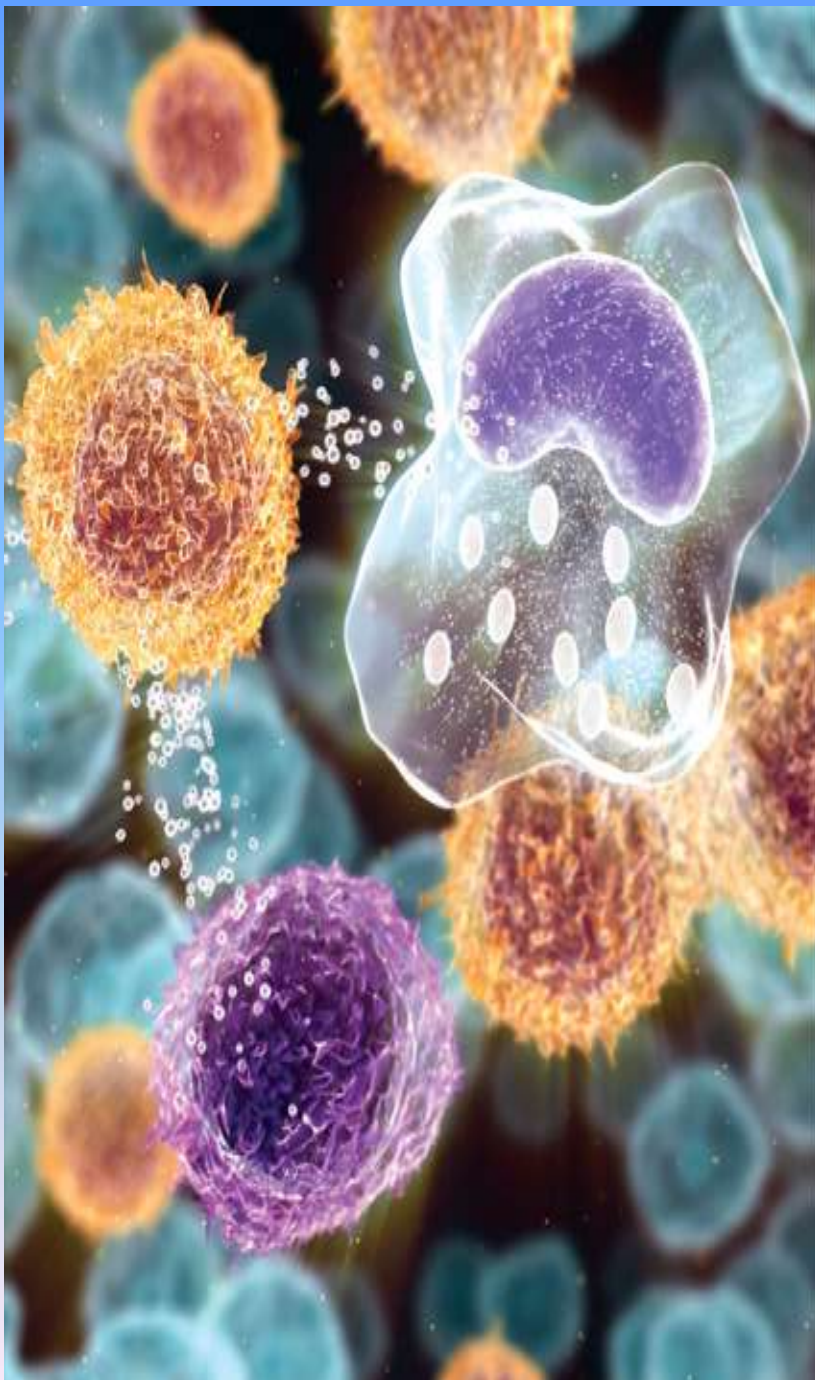
Identify polymorphisms that
regulate cognitive ability and
non-pathological decline

Genome Wide Association Study
Illumina 610 Quad microarray



Deary (2001) *Trends in Cognitive Sciences*, 5, 127-130





Cross-sectional findings

Inflammation

HLA-DRB1, HLA-DQA1
IL1R1, TLR3

Age related?

Inflammatory markers increased
in older people

Cognitive decline, Heart disease,
Dementia, Depression

Microglia switch from benign to
aggressive

Express MHC, Cell ↑ size/density
↑ synthesis of pro-Inf. Mediators

Longitudinal analysis

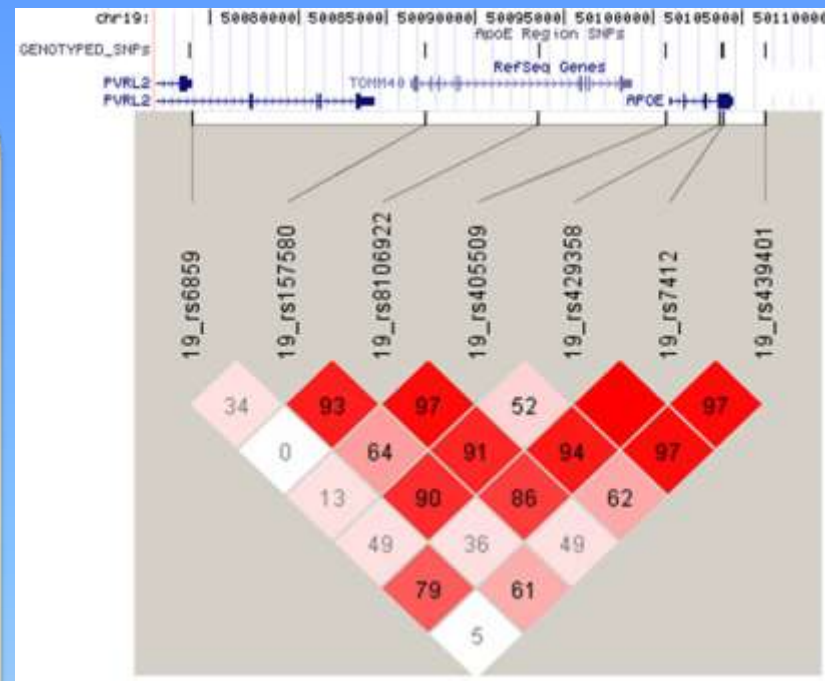
Which genes regulate the trajectory of cognitive decline?

TOMM40

TOM40 channel-forming protein import of protein precursors into mitochondria

6 kb from APOE and in very strong linkage disequilibrium

Replicated



Which gene is responsible
for cognitive decline?

APOE

TOMM40

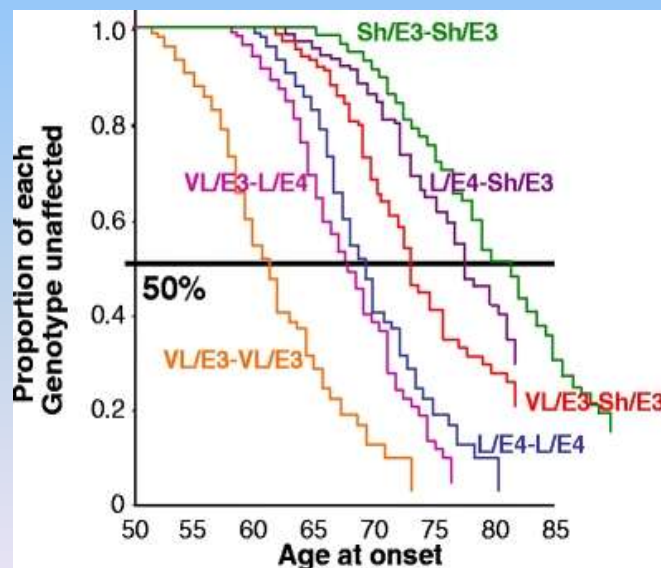
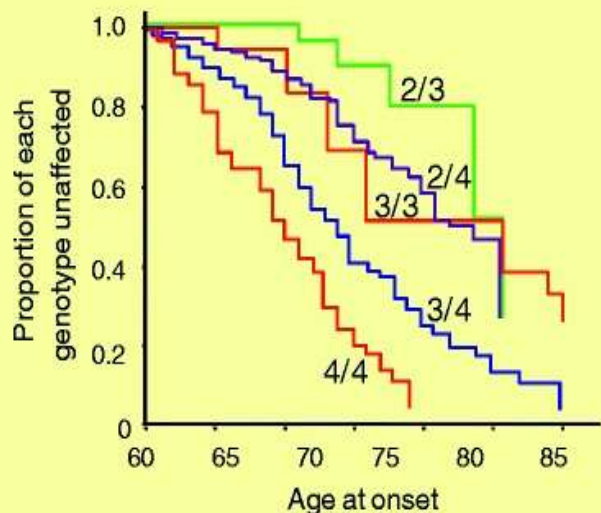
Mitochondrial dysfunction

Correlates A β /APP accumulation

APP/TOM40 form stable complexes

TOM40 moves A β into mitochondria
promoting neurotoxicity

TOMM40 poly T repeat divides
APOEe3 into high (very long) and
low risk (short) variants



Grossman et al. 2010



What next?

Follow-up GWAS data

APOE genotyping

TOMM40 Poly T genotyping

TOMM40 SNPs

Collaborative studies

NeuroCHARGE

Cognitive Working Group

($n = 30634$; Matt Keller)

Replication of findings

Generation Scotland

Mensa



26,000 members in UK
IQ>133+ (top 2% of population)

Using extreme end of the
distribution ↑ power

BBC NEWS **LIVE** BBC NEWS CHANNEL

Last Updated: Wednesday, 16 February, 2005, 16:34 GMT

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Mensa to help dementia research

The brainiest people in Britain are being enlisted by scientists for research to beat dementia.

Researchers from the University of Manchester want DNA swabs from members of Mensa, the society for people whose IQ falls within the top 2% of the UK.

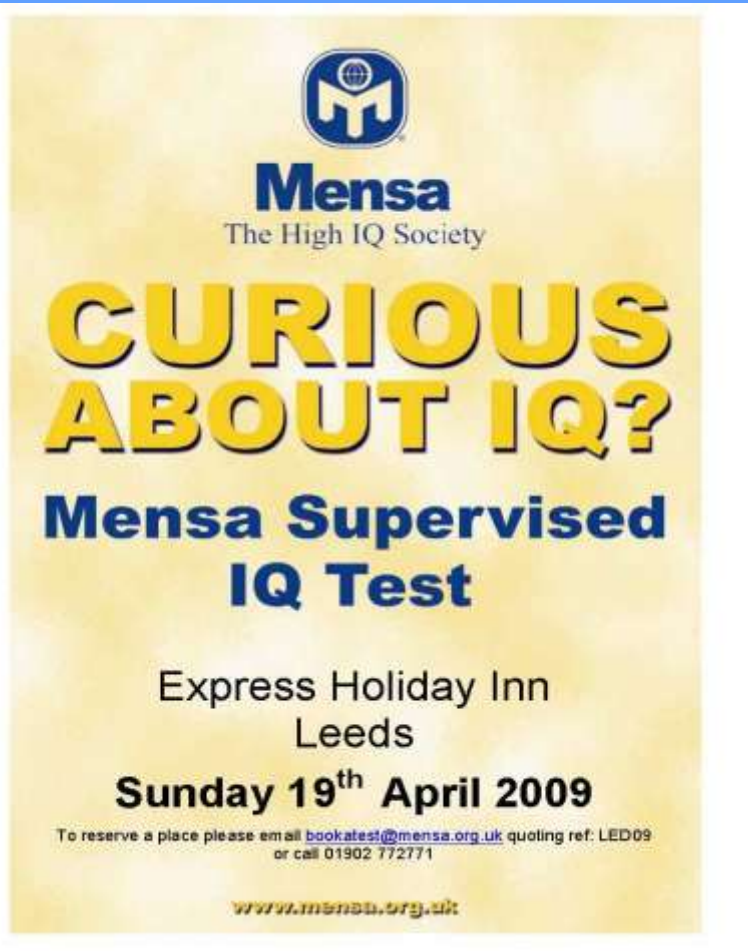
They hope to find the genes linked to intelligence and examine how they interact with each other.

More than 2,000 swab kits will be sent to Mensa members in the North West in the society's monthly magazine.

News Front Page
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Also in the news

Pilot study conducted
in NW England

Advertised in regional
Mensa magazine (2000 distr.)
>800 responses



Further Collection?

Original collection:

Cheap and cheerful

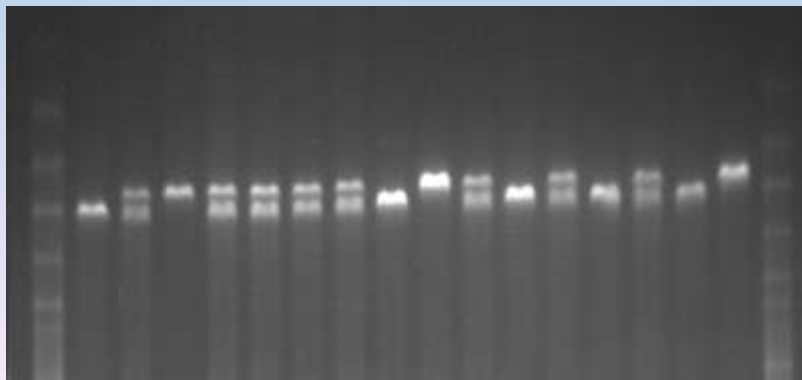
Demonstrated:

Collect via post
Store

Genotype DNA
Develop Online
Questionnaires

Country wide collection

Plans to collect 10k
samples from the UK



Summary

Ethical considerations
Treatments for cognitive
ageing research priority

Findings

TOMM40-APOE

New study designs required?

Collaborations

Tens of thousands



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