



# *Use of Twin Studies for Genomic Medicine*

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# TWINS: HOW MANY?

- Overall 1 in 50 Europeans is a twin

- MZ rates constant 4/1000 births

- No clear effect of age or race

- DZ rates vary -

Europeans 8/1000

Asians 2/1000

Bl. Africans 15/1000

- DZ rates with age: (4 fold age 37)

- Rates increasing due to infertility Rx



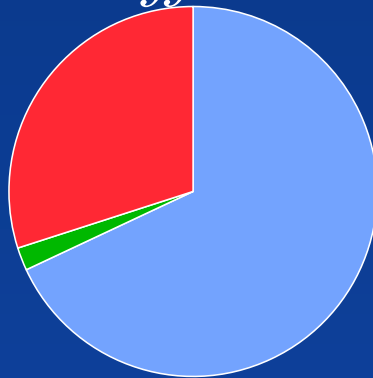
# POTENTIAL USE OF TWINS FOR GENETIC RESEARCH

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- Classical twin study - heritability
- Sib pair linkage studies
- Sib pair Association studies
- Gene- Environment interactions
- Gene Expression studies
- MZ discordant studies –CNV, epigenetics
- Pharmaco-genomics
- Aging Research
- Forensics

# HERITABILITY ESTIMATES

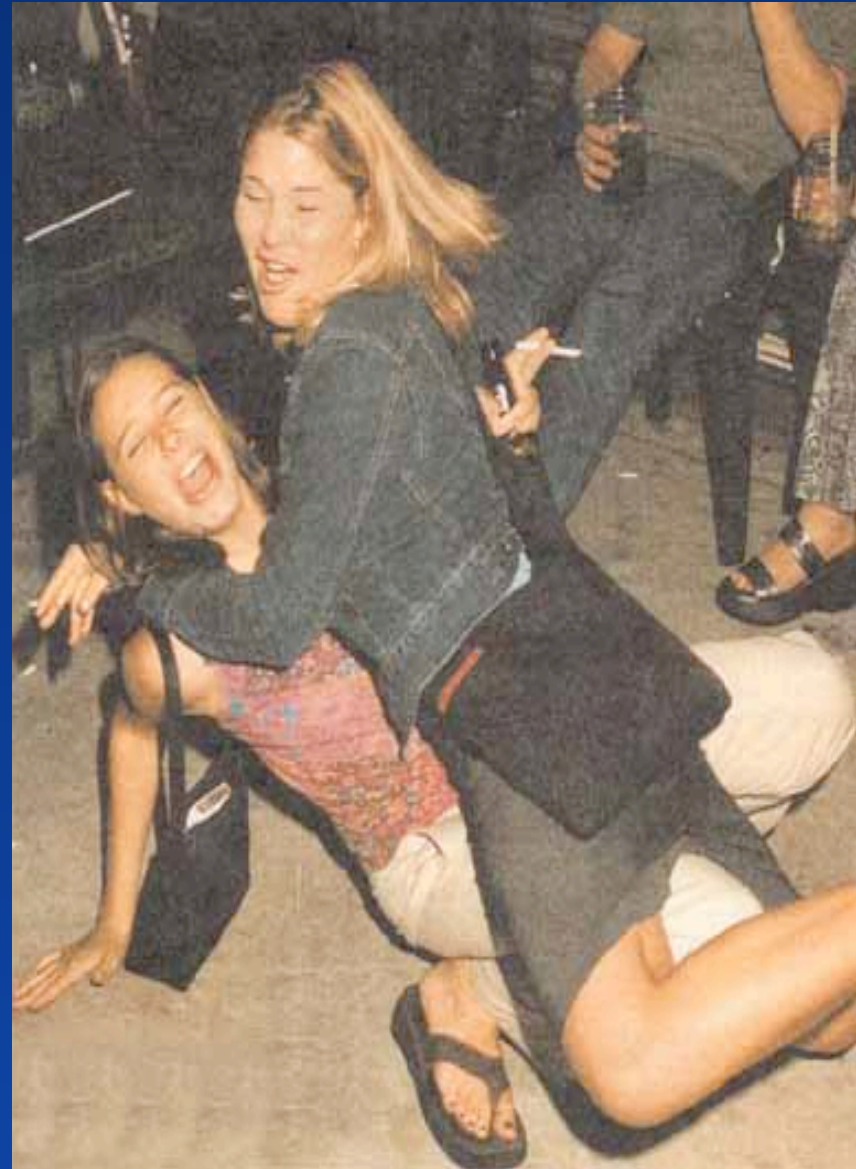
*“The proportion of differences between individuals explained by genetic differences.”*



# TwinsUK Adult Twin Registry


- 11,000 Twin volunteers recruited through media campaigns
- Healthy Representative adult population 18-85
- 85% female
- 7500 –(3000 MZ and 4500 DZ) twins seen clinically with DNA
- 6000 have GWAS (317 or 610K)
- 1300 Stored PBLs
- LCL GW expression on 1200 twins, 850 fat, 850 skin, 100 muscle ongoing.
- Longitudinal DNA, serum & urine stored
- 1000s of phenotypes - longitudinal





# HERITABILITY OF COMMON TRAITS

<b>FRECKLES</b>	<b>90%</b>	
<b>Myopia</b>	<b>90</b>	<b>HIGH</b>
<b>ACNE</b>	<b>80</b>	
<b>HEIGHT</b>	<b>80</b>	
<b>OSTEOPOROSIS</b>		<b>75</b>
<b>DIABETES</b>	<b>70</b>	
<b>OBESITY</b>		<b>70</b>
<b>BLOOD CLOTTING</b>	<b>70</b>	
<b>BACK PAIN</b>	<b>65</b>	
<b>IQ</b>	<b>65</b>	
<b>ASTHMA , allergy</b>	<b>60</b>	
<b>ARTHRITIS (OA)</b>	<b>60</b>	
<b>CATARACT</b>	<b>60</b>	
<b>MOTION SICKNESS</b>	<b>60</b>	
<b>Naevus count</b>	<b>55</b>	
<b>Pain thresholds</b>	<b>55</b>	
<b>Migraine</b>		<b>50</b>
<b>Varicose veins &amp;HR</b>	<b>50</b>	
<b>Menopause</b>	<b>50</b>	
<b>Blood pressure</b>	<b>50 %</b>	
<b>Menarche</b>	<b>40%</b>	<b>LOW</b>



# Heritability of blood levels- using TwinsUK

- CRP, IL-6 –40%
- Vitamin D –40%
- Factor V, VIII, XIII- 70%
- Collagen cross links-50%
- Alkaline phosphatase –75%
- Creatinine- 50%
- Platelet count- 65%
- CD4/CD8 ratios -60%
- White Cell apoptosis rates 65%
- Platelet counts- 50%
- Leptin - 70%
- Glucose 51%
- Insulin 60%
- HOMA 57%
- HbA1c 60%
- T4, T3 63%
- Telomere length 40%
- HbF – 50%
- WCC- 55%
- Response to folate- 55%**



# HOW HERITABLE IS CANCER?

<b>PROSTATE CANCER</b>	<b>40 %</b>
<b>BREAST CANCER</b>	<b>25</b>
<b>LUNG CANCER</b>	<b>25</b>
<b>OVARIAN CANCER</b>	<b>22</b>
<b>CERVIX CANCER</b>	<b>0%</b>
<b>WOMB CANCER</b>	<b>0%</b>
<b>KIDNEY CANCER</b>	<b>0 %</b>

Lichtenstein et al 2000 – Joint Scandinavian twin registries

# Personality traits

OCEAN

40-50% H2

<10% C

- Obsession
- Conscientiousness
- Extroversion
- Anxiety
- Neuroticism

## Genetics of taste and smell

	h <sup>2</sup>	
Bitter taste – PTC	100%	Drayna 2003
Food neophobia	65%	Knaapila 2007
Emotional eating <sub>(TFEQ)</sub>	44%	Knaapila 2007
Sweet taste pref	53%	Keskitalo 007
Androstenone perception	28%	Knaapila 2008
Fruit and Veg diet	49%	Teucher 2008
Garlic eating	48%	Teucher 2008
Coffee	41%	Teucher 2008
Red meat	39%	Teucher 2008

# Obesity or lifestyle? Studies in twins separated at birth



Dizygotic Twins



Monozygotic Twins

Borjeson, Acta Paed. 1976

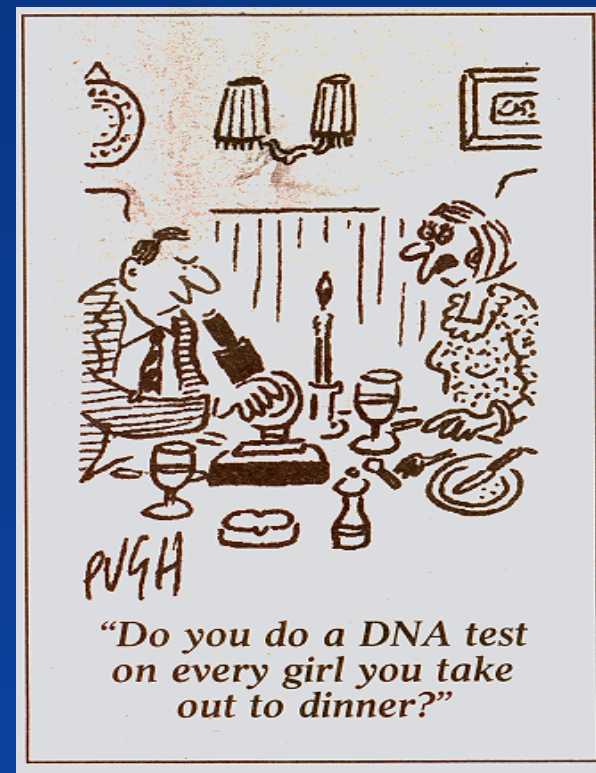
# Non Heritable traits

	H2
Church attendance	0
Milk Chocolate preference	<10
Football team support	<10
Liking mister Bean	0
Miscarriage rates	0

# SOCIO-SEXUAL TRAITS FOUND TO BE GENETIC

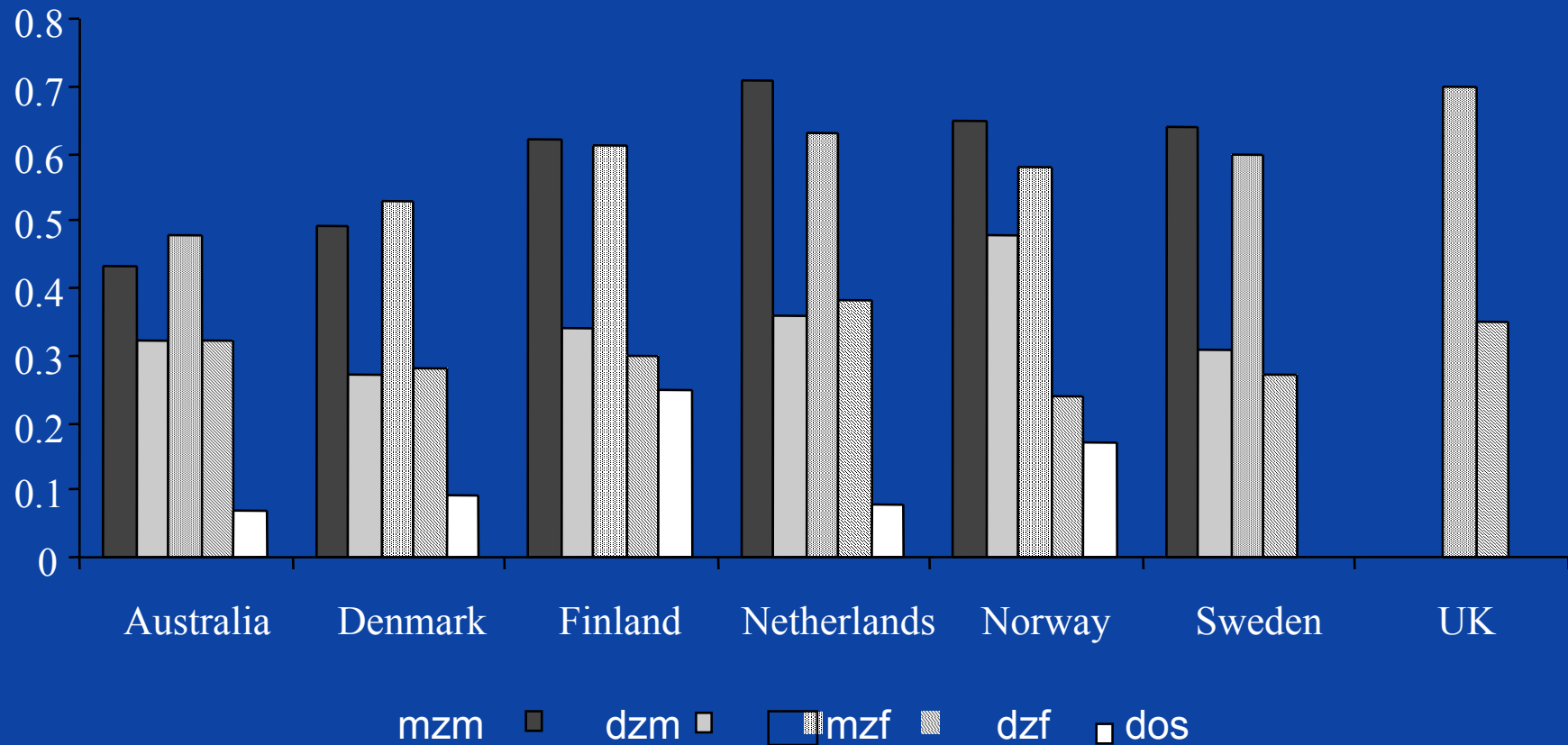
- Divorce
- Jealousy
- Infidelity
- Male homosexuality
- Female homosexuality
- Libido
- Promiscuity
- Female orgasm
- Body odour

# Genes and sexual function



# EXERCISE AND GENES

Twin correlations for exercise participation by country and zygosity group (GenomEUtwin)



deGeus 2007



# ‘Environmentally’ Genetic Traits

- Exercise
- Smoking
- Alcohol
- Occupation
- Social class
- Marital Status
- Food Preference - taste
- Dietary habits



- Religiosity and the belief in God have been found in Europe and USA to be under modest genetic influence (30-50%)
- Belief or scepticism are genetic traits.....

# Genome-wide expression- A new phenotype?

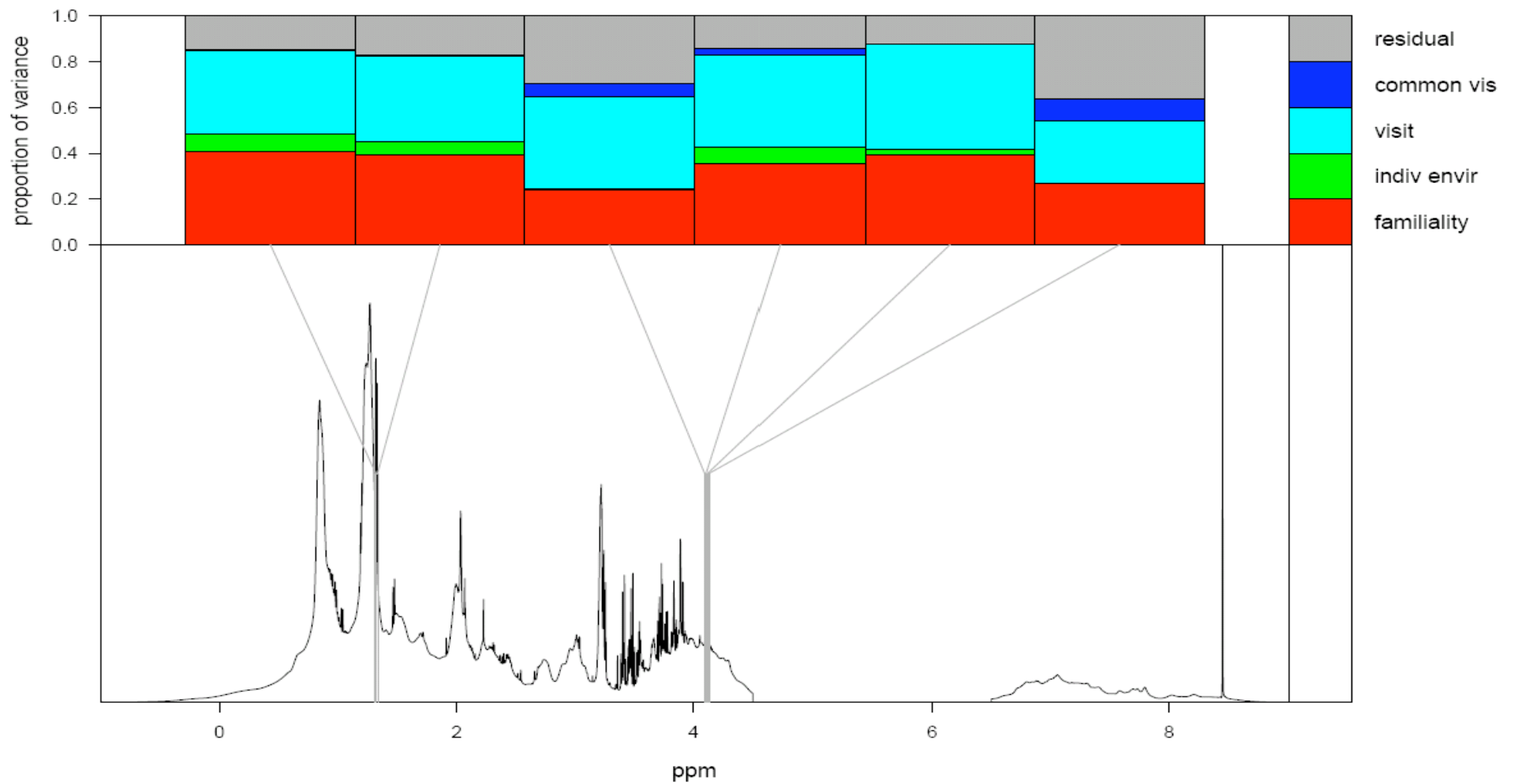
- Dixon et al (Nature Genetics 2007)
  - Goring et al - Nat Gen 2007
  - Valur et al - Nature 2008
  - Min et al – in preparation
1. Approx 30% of expressions heritable
  2. Wide variation in genetic influence
  3. The more heritable the more eQTLs associated
  4. The more heritable the more pleiotropy between tissues

# Metabolomics in 150 twins

lactate

nmr moltwin plasma, 1d pulse sequence

moltwin variance components



# Discordant Identicals: Olivia & Isabelle (ALL)



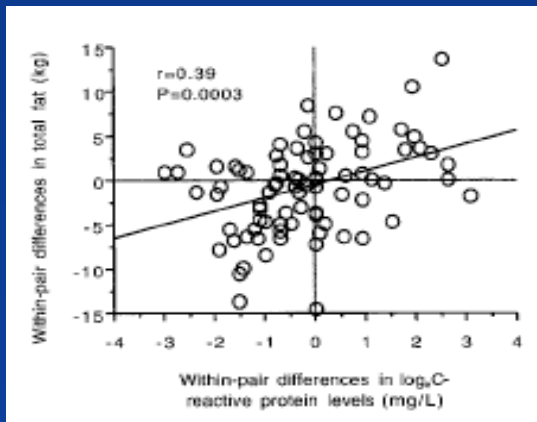
Hong et al Science. 2008 Jan  
18;319(5861):336-9.

## Discordant Birthweight Twins.



- **Lipids**- Negative Association between twin pairs only and not within pairs -Suggests that shared influences on the maternal environment important  
*Skidmore et al. (2006)*
- **BP** - negative association within twin pairs –suggesting fetal malnutrition may be important.  
*Poulter et al 2000*

# The Association Between C-Reactive Protein and Obesity/central fat in MZ Female Twins



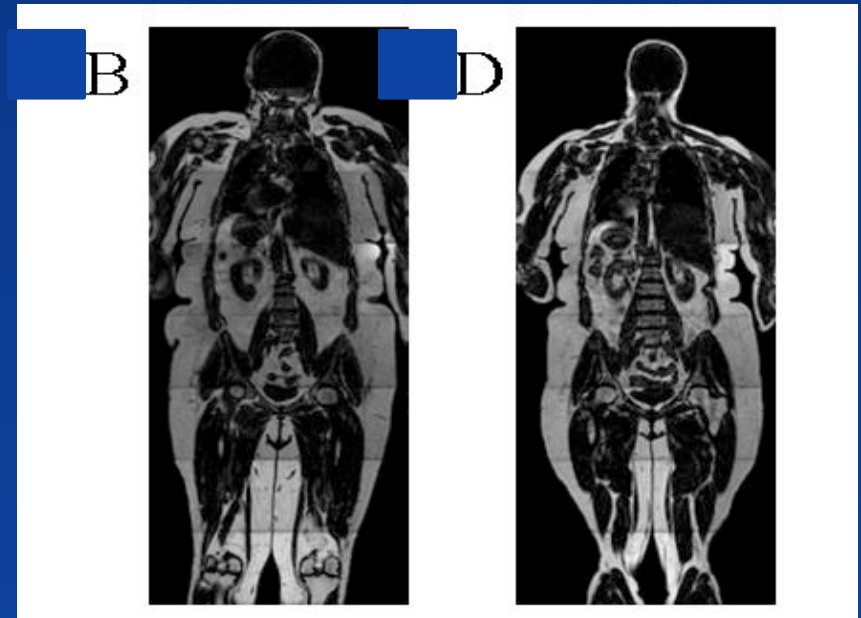
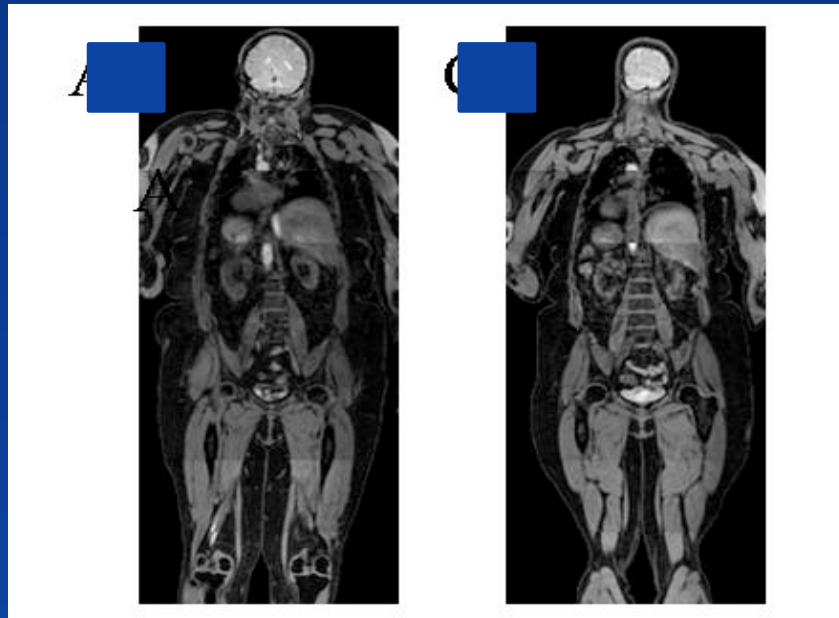
CRP was strongly related to total and central abdominal obesity, lipid levels and blood pressure independent of genetic influences (controlled for by MZ twin analysis).

So effect **not** cause

# Deep phenotyping- Body water and fat distribution in discordant twins

body water

fat



T1 (BMI 47) T2 (BMI 32)

T1 (BMI 47) T2 (BMI 32)



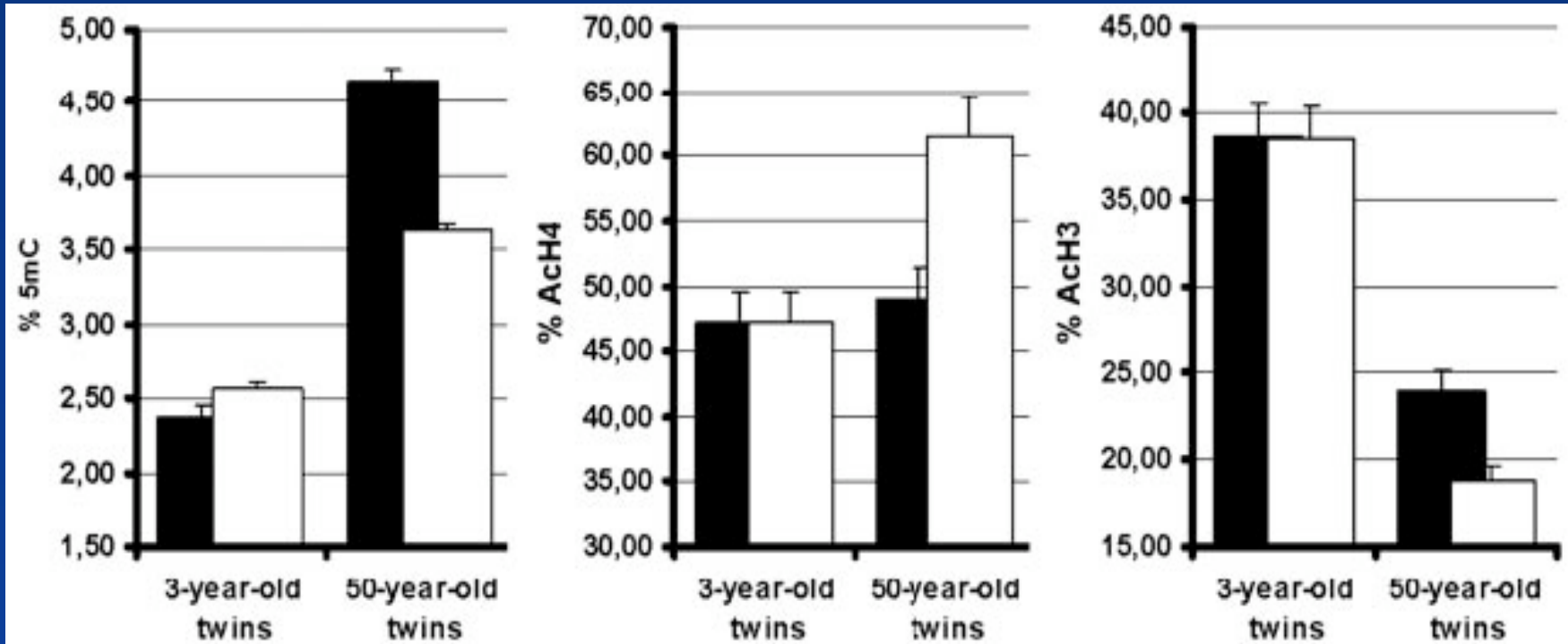
# Where is the missing heritability?

- GWAS hits explain 1-10% of genetic variance
- MZ Twin discordance unexplained by known environmental factors
- Could Epigenetic factors be responsible??



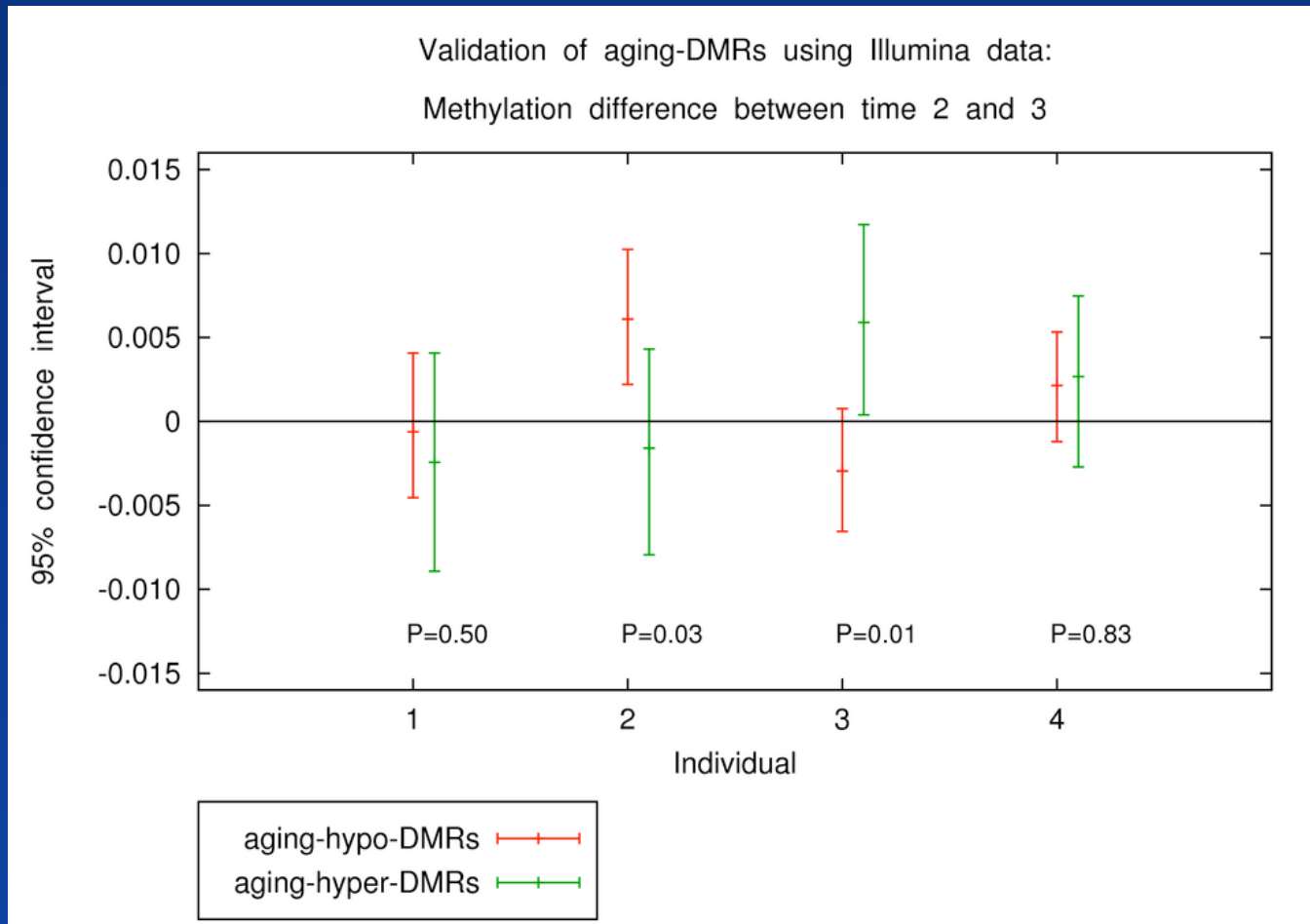
MZ twins – a natural RCT

# Epigenetics in MZ twins



Fraga et al PNAS 2005

# Methylation in twins over time

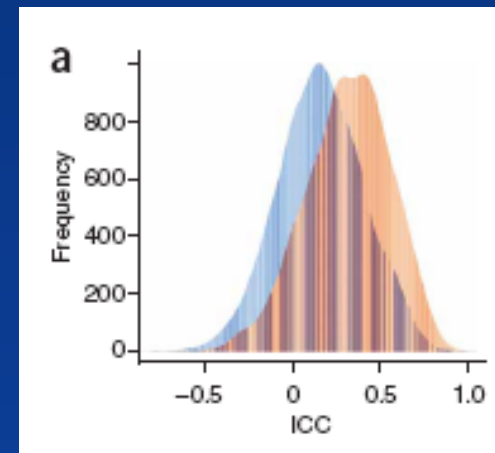


Rakyan et al (in preparation)

# Methylation in Twins

- MZ Twins show greater concordance for total methylation at different tissue sites, LCL, buccal, bowel.
- Areas under most genetic control are those close to promotor regions of functional importance.

– Kaminsky et al Nature Genetics 2009



Buccal:  
MZ= red, DZ= blue

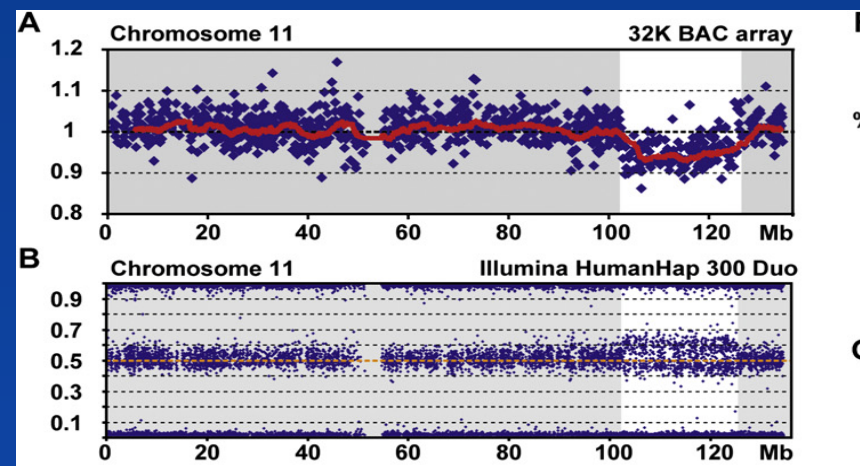
# Copy Number Variation differences in MZ twins

- A study of 19 pairs of MZ twins showed a proportion with CNV differences

Any differences in the genetic makeup between twins derived from the same zygote represent an irrefutable example of somatic mosaicism..

Suggest that CNV analysis in phenotypically discordant monozygotic twins may provide a powerful tool for identifying disease loci.

Bruder et al AJHG 2008



## Forensics and twins

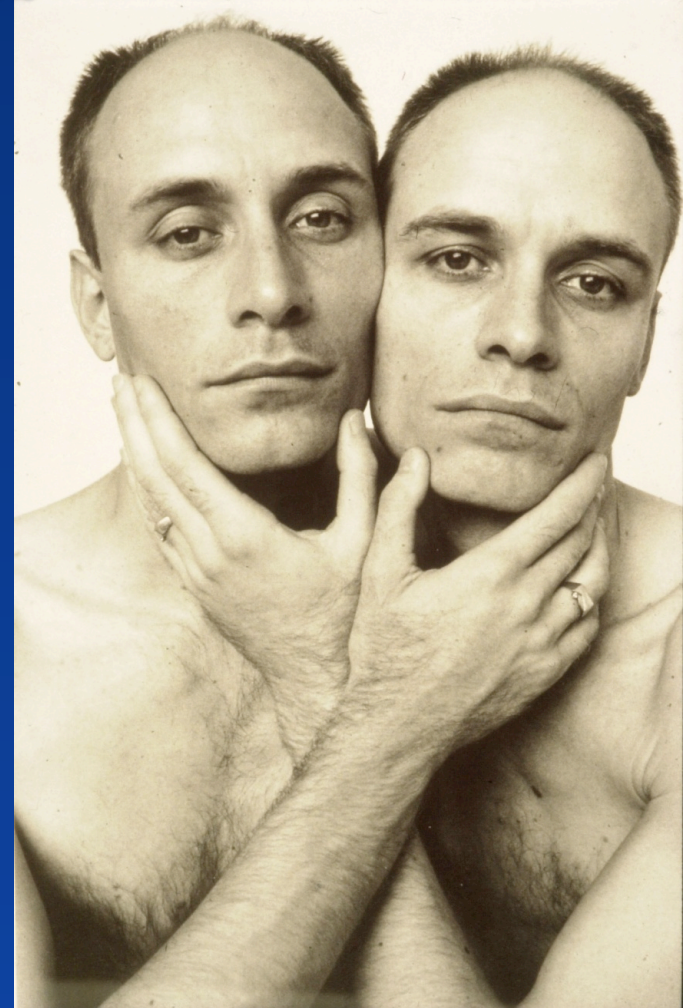


- Identical twins are identically innocent and guilty... march 2009
- Saved by their indistinguishable DNA, identical twins Hassan and Abbas O suspected in a \$5 mil jewelry heist have been set free. Neither could be exclusively linked to the DNA evidence.

# Getting to the Root of Hair loss

- Highly heritable >80%
- Common – 1 in 4 men early
- Collaborative study-
  - GSK, Decode, TwinsUk, Nijmegen
- Using 1,125 men identified a new locus at chr 20p11.22, confirmed in 3 independent cohorts (P $\times$ 10<sup>-14</sup>)
- The one man in seven who harbours risk alleles at both 20p11.22 and AR has a sevenfold-increased odds of androgenic alopecia (OR 7.12)

Richards et al 2008 Nature Genetics





# Current Collaborative Twin GWAS

- GWAS on 6000 twins (illumina 317 & 610k)
  - Bone –BMD and fracture – (Lancet 2008 & Nature Genetics 2009 in press)
  - Metabolic/obesity –leptin, adiponectin, lipids, Nature Genetics 2008
  - HOMA, BMI, glucose, insulin (Nat Genetics 2009)
  - CVD –clotting factors, platelet counts (Nat Genetics in press)
  - HbF – Nature Genetics 2008
  - Eyes –myopia (AJHG 2008)
  - Telomere length J med Genetics (in press)
  - Naevus counts and melanoma– Nature Genetics 2009 ( in review)
  - Baldness (Nature Genetics 2008)
  - OA (AJHG 2008 and Nature Genetics 2009 submitted)
  - Menopause (Nat Genetics in press)
  - Menarche – (Nature Genetics in press)
  - Blood pressure (Nature Genetics 2009)
  - Many others ongoing , muscle, pain reporting, cataract, adiponectin, Vit D, homocysteine, handedness, ECG, exercise, entrepreneurship, etc.

# Twins and longevity



101 years – the worlds oldest

*The Times*

## UK-TWINBANK

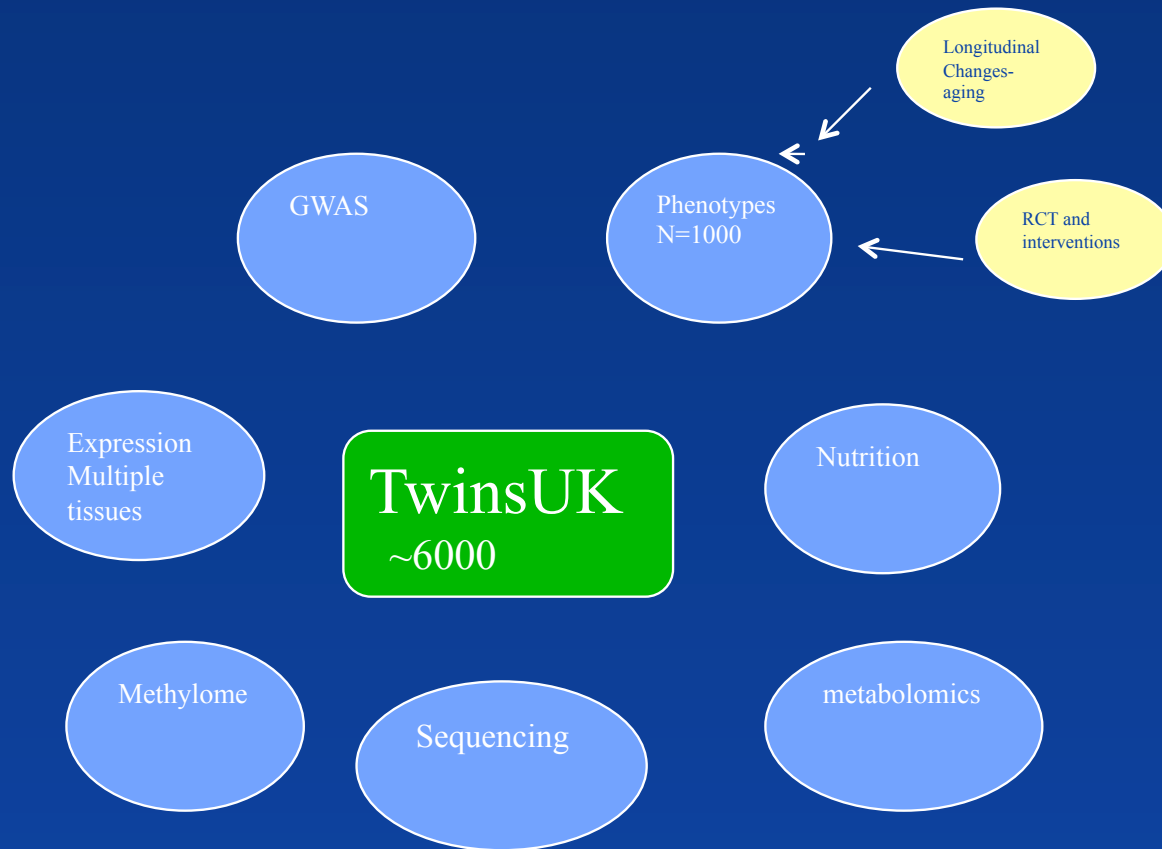
March 31, 2009

### Search for a twin solution to matters of life and death



- 620,000 twin pairs identified since 1920
- 250,000 pairs recruitable to TwinBank
- Largest in world by 5-fold
- NHS record linkage possible
- Rare diseases and drug reactions could be studied in detail
- Large numbers of discordants
- Large scale epigenetics possible
- Synergy with UK Biobank

# Twins – a complete resource



# Conclusions

- Twins are a flexible and reliable research tool
- Virtually all traits (even ‘environmental’ ones are heritable —with common /family environment having minimal effect
- Twin studies can change perceptions
- Cohorts with multiple phenotypes will continue to be rich sources of gene discovery
- Twin Biobanks- allow a unique design adjusting for genetic effects-
  - Particularly useful for epigenetics, gene-age interactions and longitudinal studies
- [www.TwinsUK.ac.uk](http://www.TwinsUK.ac.uk)

Wellcome Trust  
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BBSRC, NIH

### DTR Analysis team

Fran Williams  
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- KORA
- CHARGE
- ENGAGE
- MAGIC
- GIANT
- SUNLIGHT
- Decode
- CoLaus
- OIMR
- IV Amsterdam
- GenomEUtwin
- Global BP
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