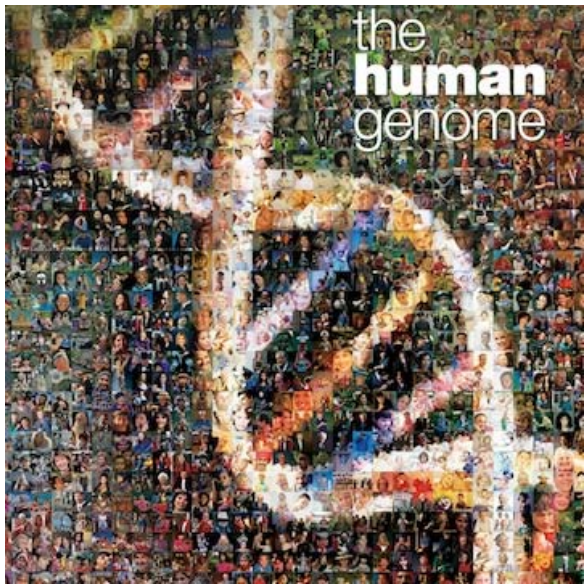
Genetic epidemiology in the genomic age:
Missing Heritability &
The Role of Twin Studies in the Genomic Era

Michel Nivard, Conor Dolan & Nick Martin

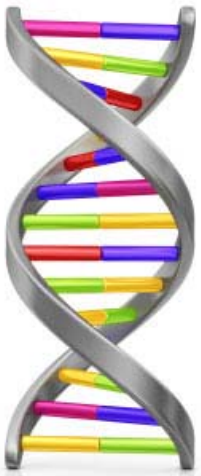
The genomic era: Mapping the genome



2001 Draft of the human genome released, 2003 final sequenced genome released.

The final genome contained ~ 3 Billion base pairs

The genomic era: Mapping the genome



The genomic era: Mapping genomic variation

2005-10-24: **HapMap Public Release #19**
Genome sequence for 270 individuals
4 populations

Human genome project: GCTATCGATCACT

HAPMAP:

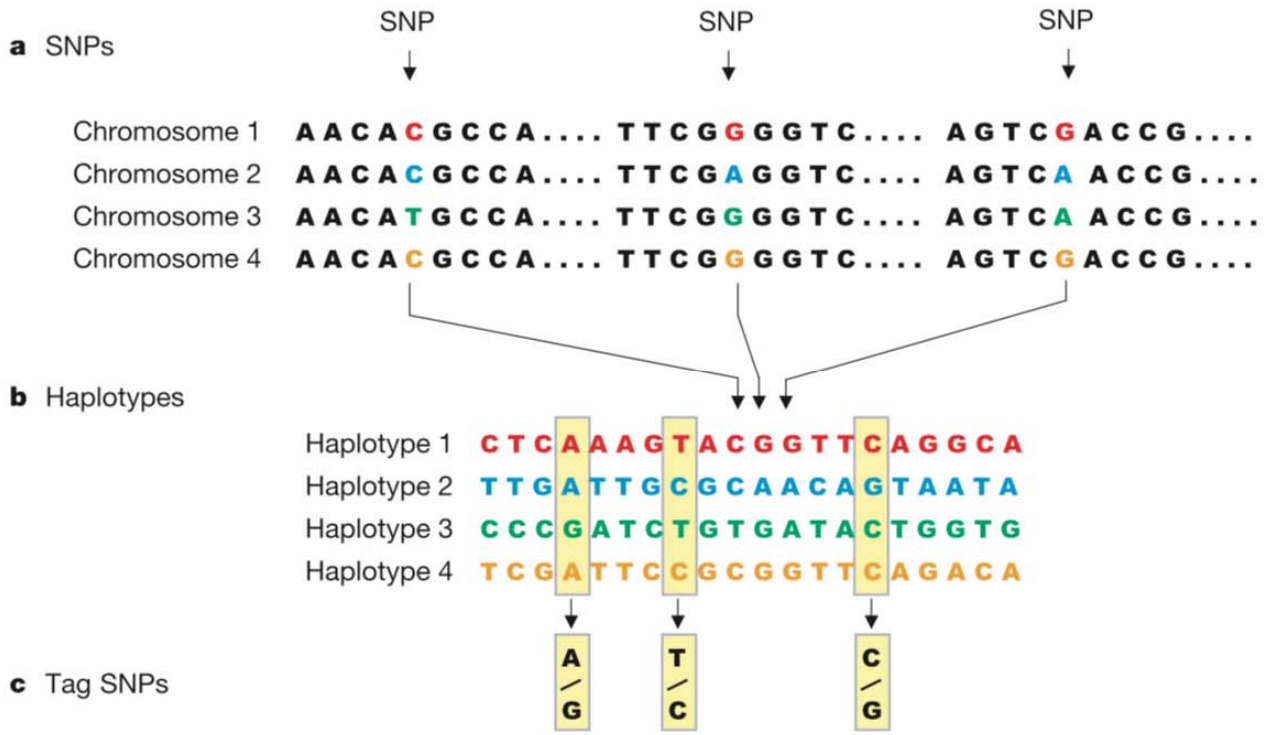
GCTATCGATCACT

GCTATCGGTCACT

GCTATCGATCACT

GCTATCGGTCACT

The genomic era: Mapping genomic variation

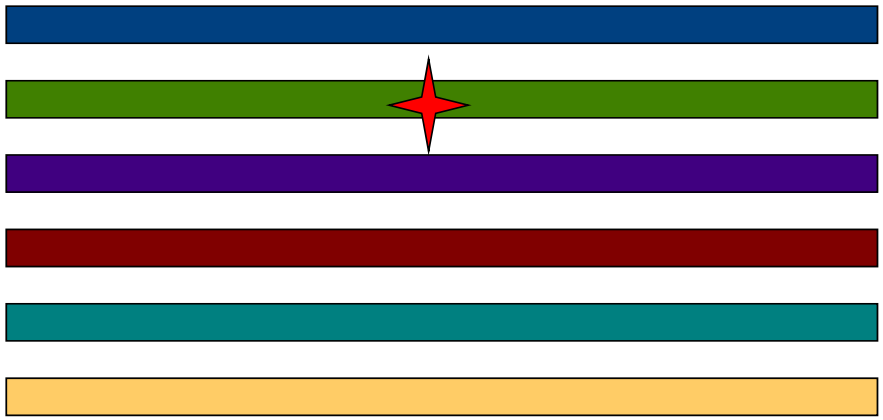


The International HapMap Consortium figure-1 Nature (200

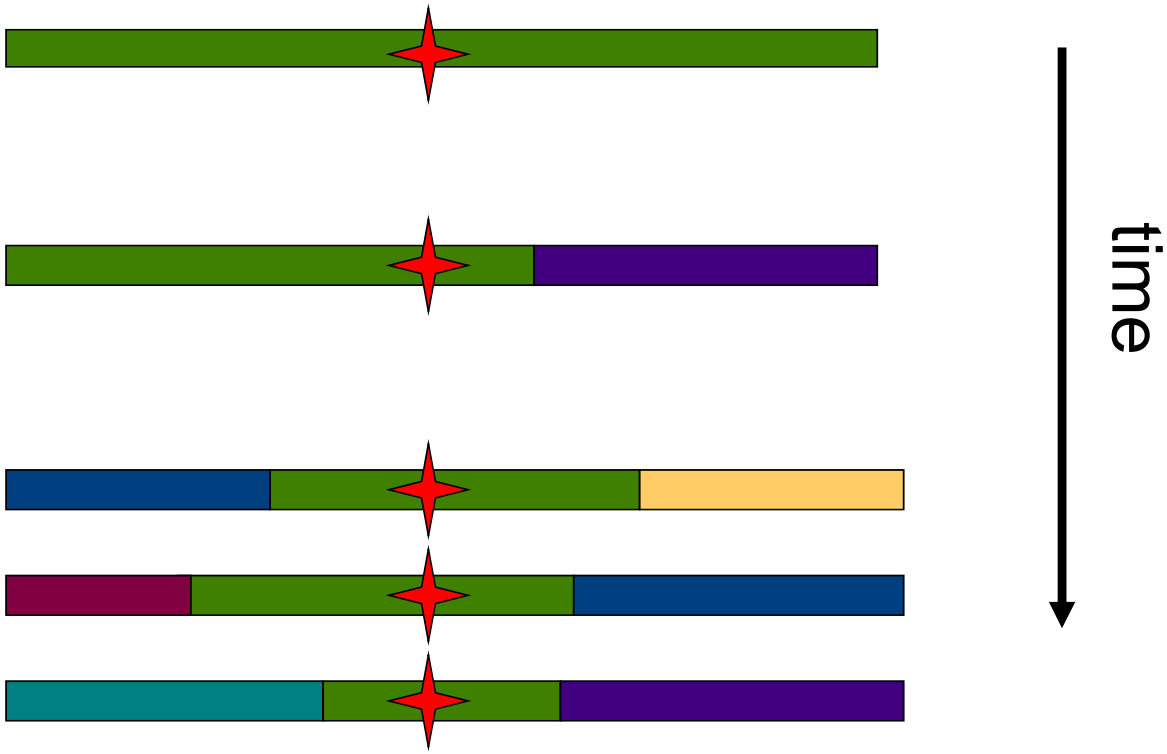
The genomic era: genotyping tag SNPs

how many angels on the head of a pin? I don’t know

The genomic era: Mapping genomic variation



The genomic era: Mapping genomic variation



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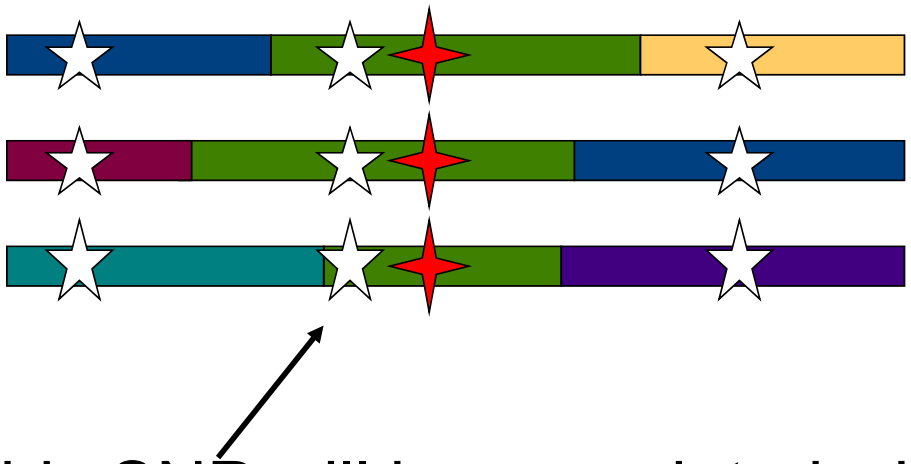
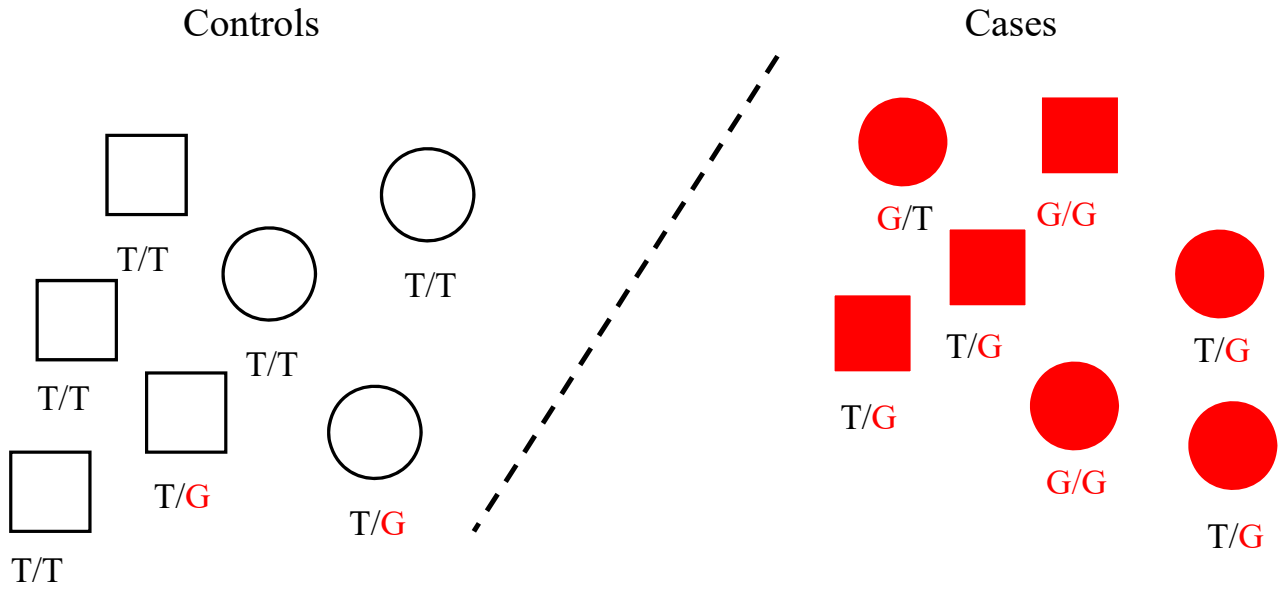


The genomic era: Case control studies



Allele G is ‘associated’ with disease

The genomic era: Case control studies

- Each individual contributes two counts to 2x2 table.
- Test of association

$$X^2 = \sum_{i=0,1} \sum_{j=A,U} \frac{\left(n_{ij} - E\left[n_{ij}\right]\right)^2}{E\left[n_{ij}\right]}$$

where $E\left[n_{ij}\right] = \frac{n_{i\cdot} n_{\cdot j}}{n_{\cdot\cdot}}$

	Cases	Controls	Total
G	n_{1A}	n_{1U}	$n_{1\cdot}$
T	n_{0A}	n_{0U}	$n_{0\cdot}$
Total	$n_{\cdot A}$	$n_{\cdot U}$	$n_{\cdot\cdot}$

- X^2 has χ^2 distribution with 1 degrees of freedom under null hypothesis.

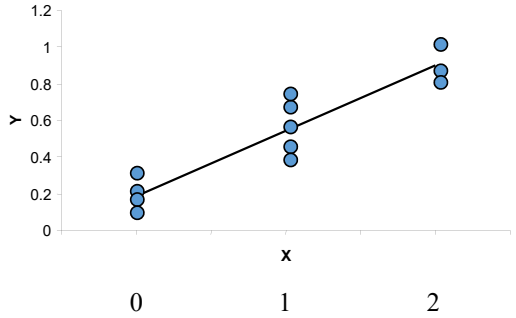
The genomic era: continuous phenotype

$$Y_i = \alpha + \beta X_i + e_i$$

where

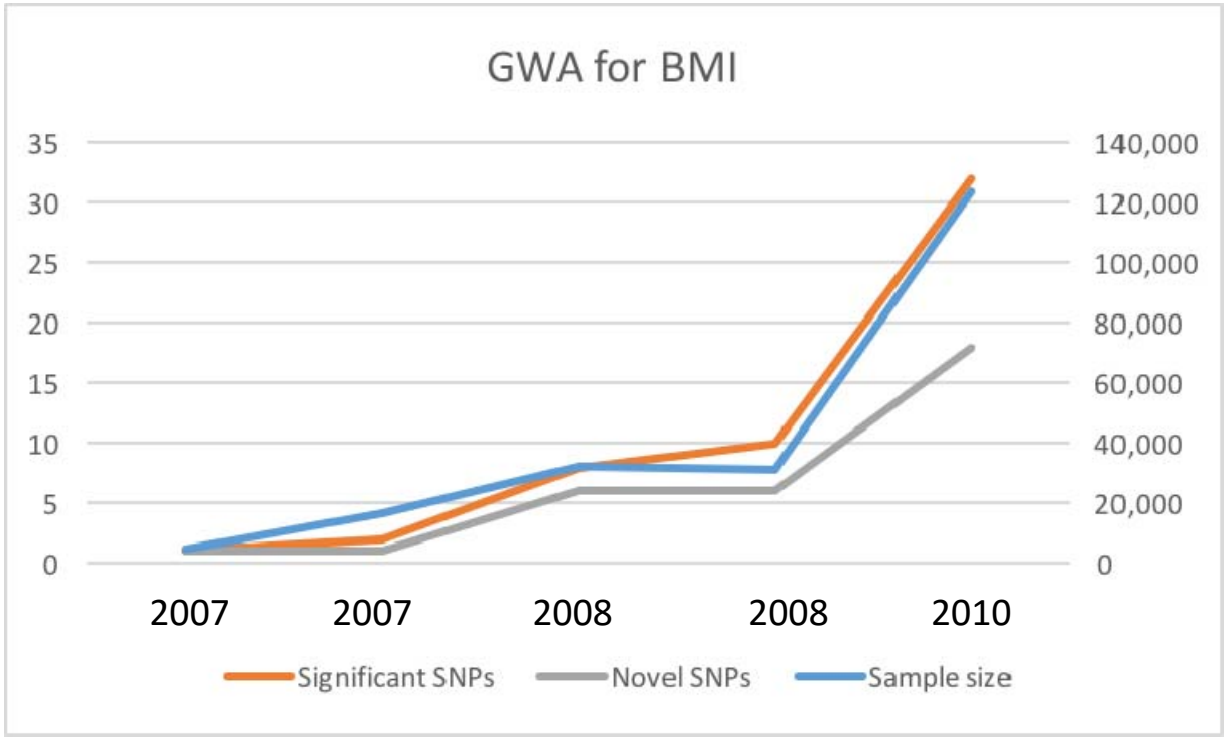
Y_i = trait value for individual i

X_i = number of 'A' alleles an individual has



Association test is whether $\beta \neq 0$

The genomic era: BMI



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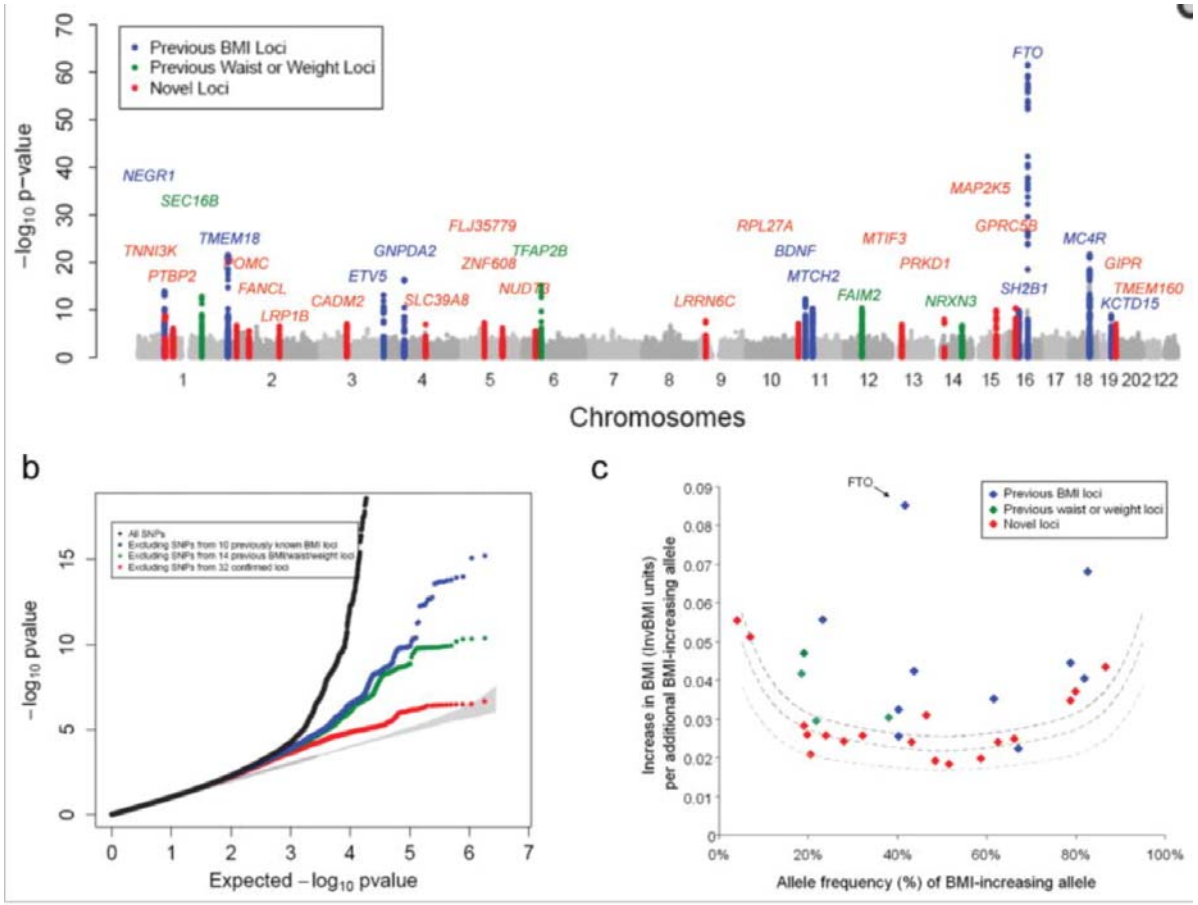


The genomic era: “Missing“ heritability

B. Maher The case of the missing heritability
Nature 2008

The genomic era: “Missing“ heritability

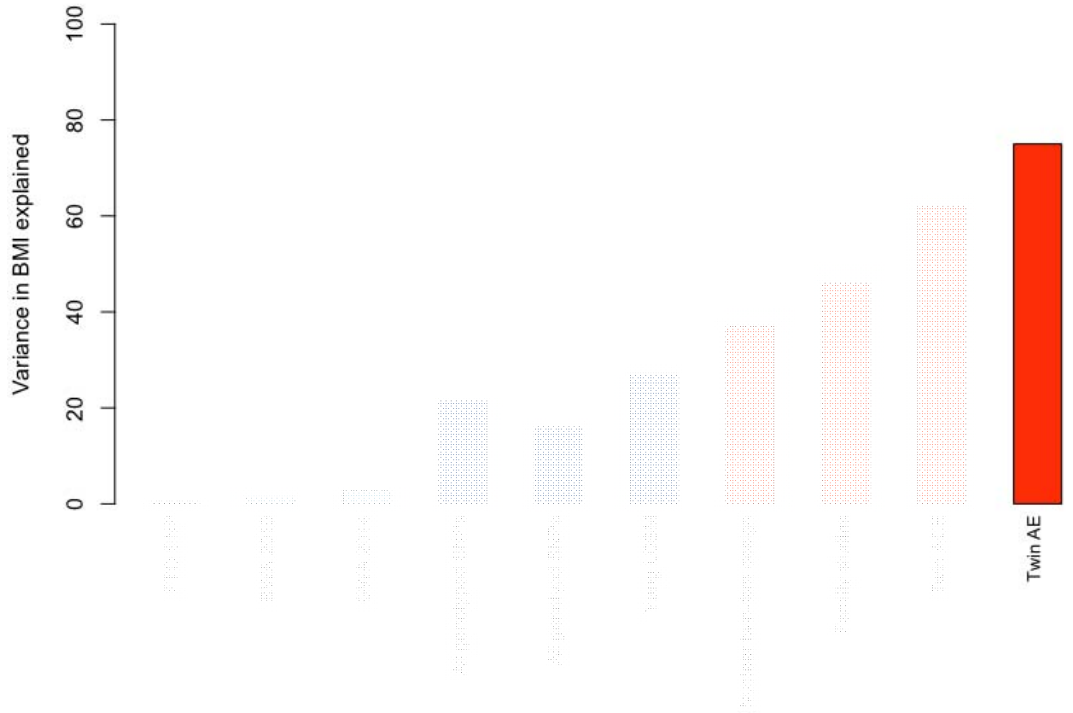
The variance explained by genotyped loci related to complex traits, is substantially smaller than the additive genetic variance estimated in twin studiers of the same traits

$$h^2_{missing} = 1 - (\frac{R^2_{snp}}{h^2})$$

B. Maher The case of the missing heritability Nature 2008

“Missing” heritability: BMI

Elks et al (2012) Meta analysis of twin studies:
Variance in BMI explained by additive genetic effects:
75% (74%-76%)



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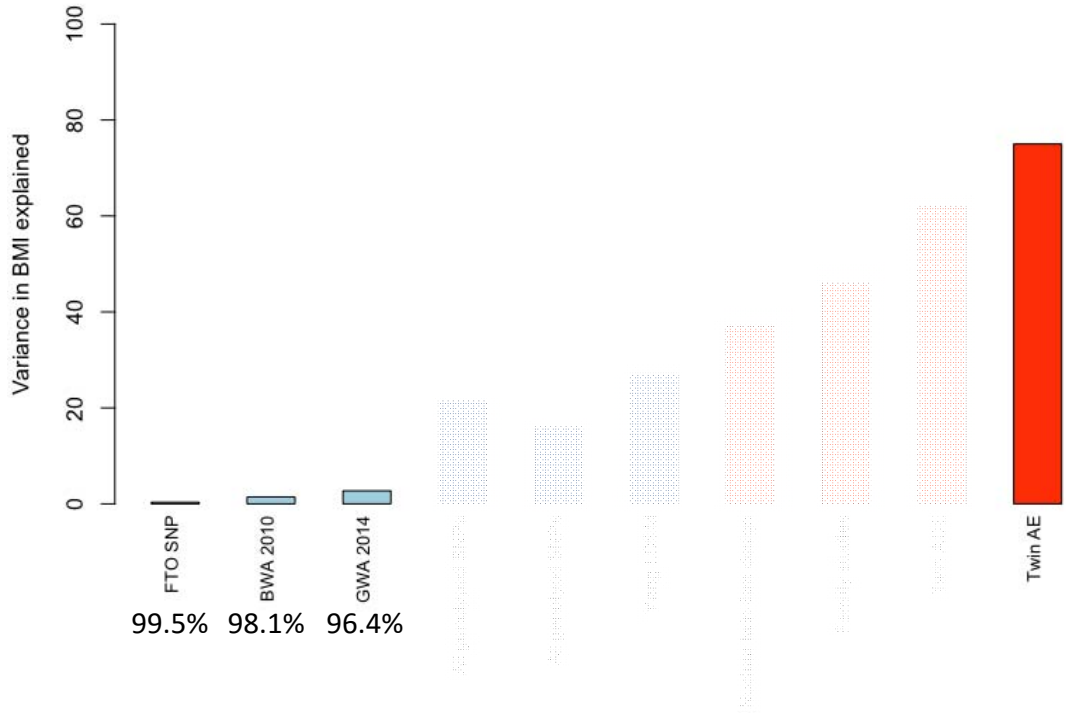
Strongest locus: **0.34%** of variance in BMI
All significant loci(32): **1.45%** of variance in BMI



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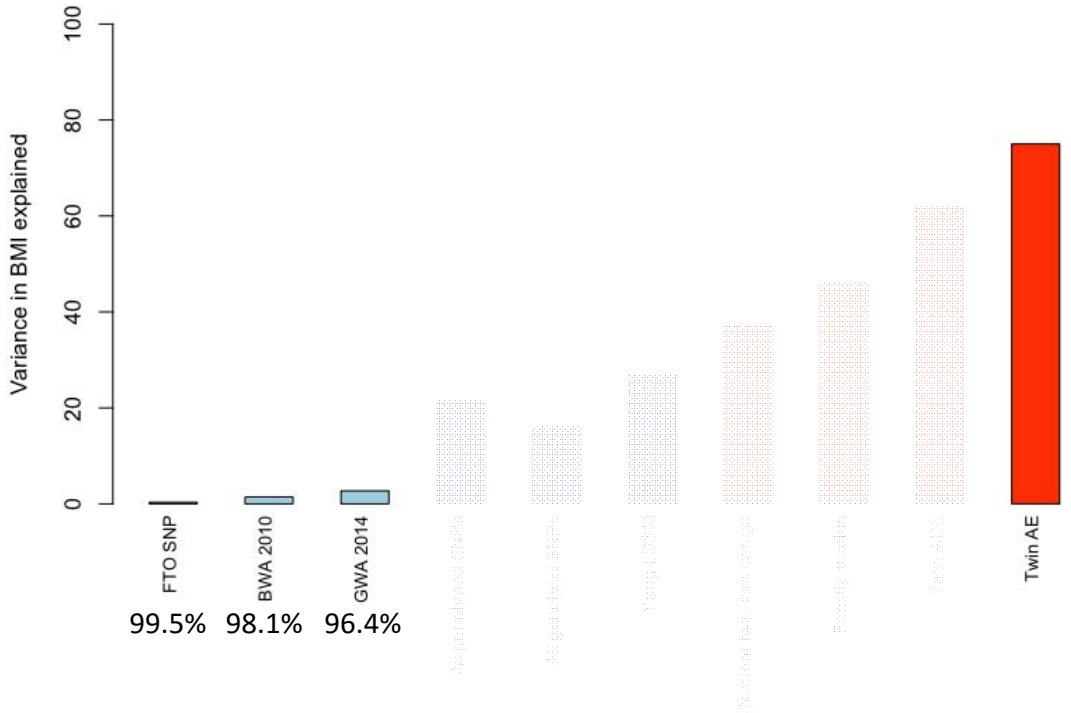

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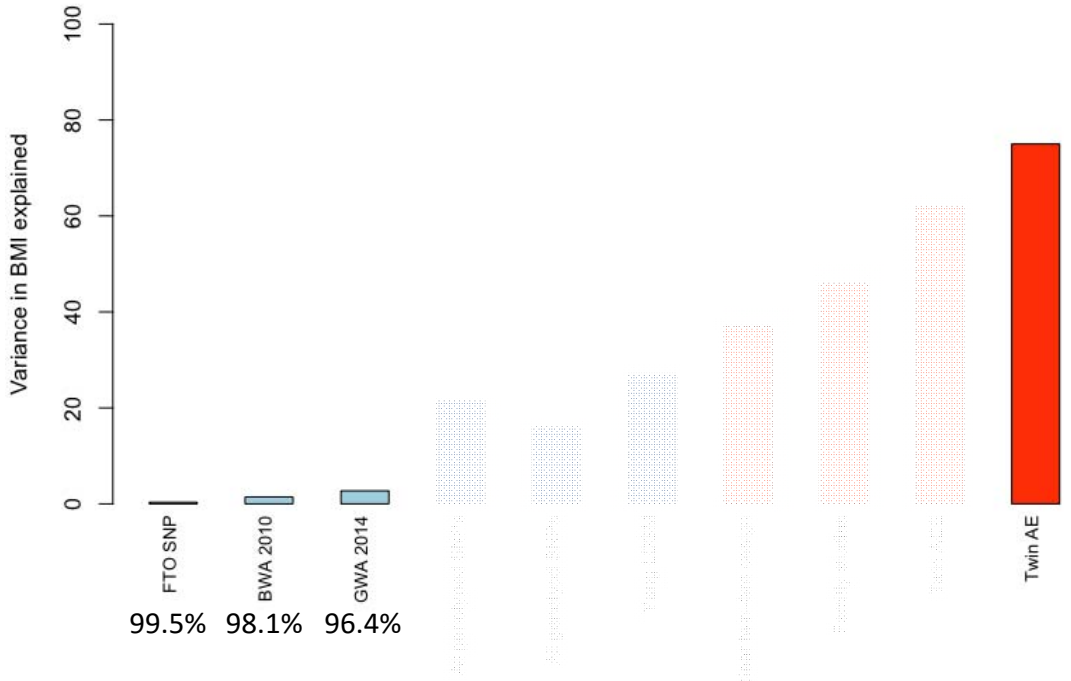

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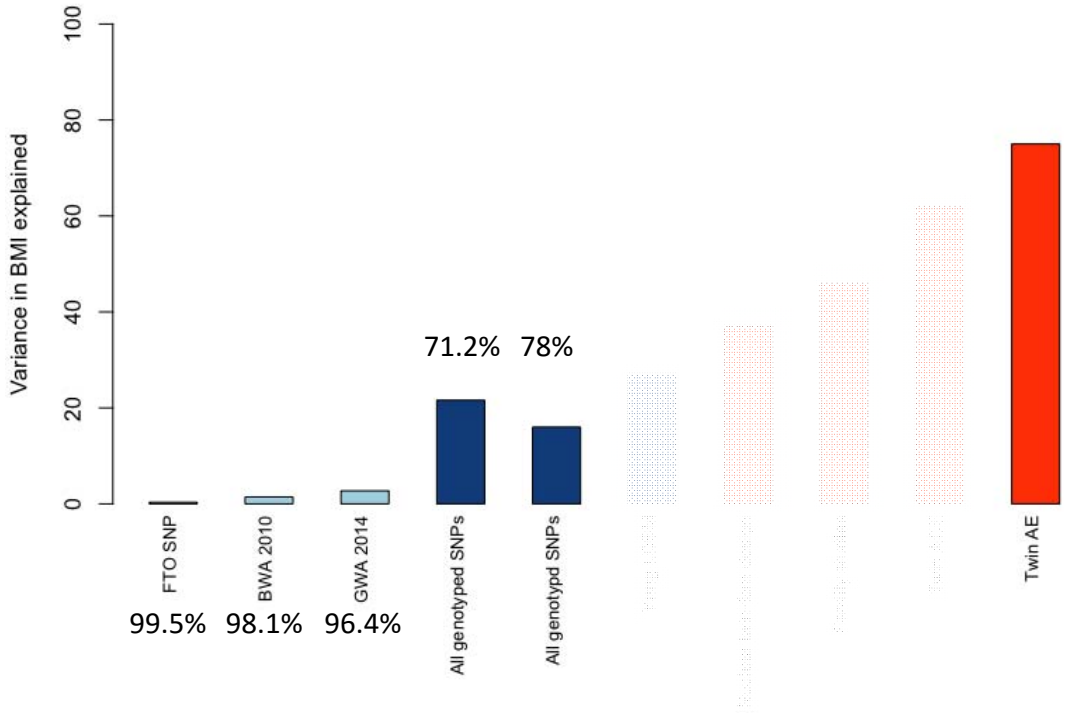
Yang et al (2012) GCTA:
16.5% of variation in BMI explained by genotyped SNPs

Lock et al (2015) GCTA:
21.6% of variation in BMI explained by measured SNPs



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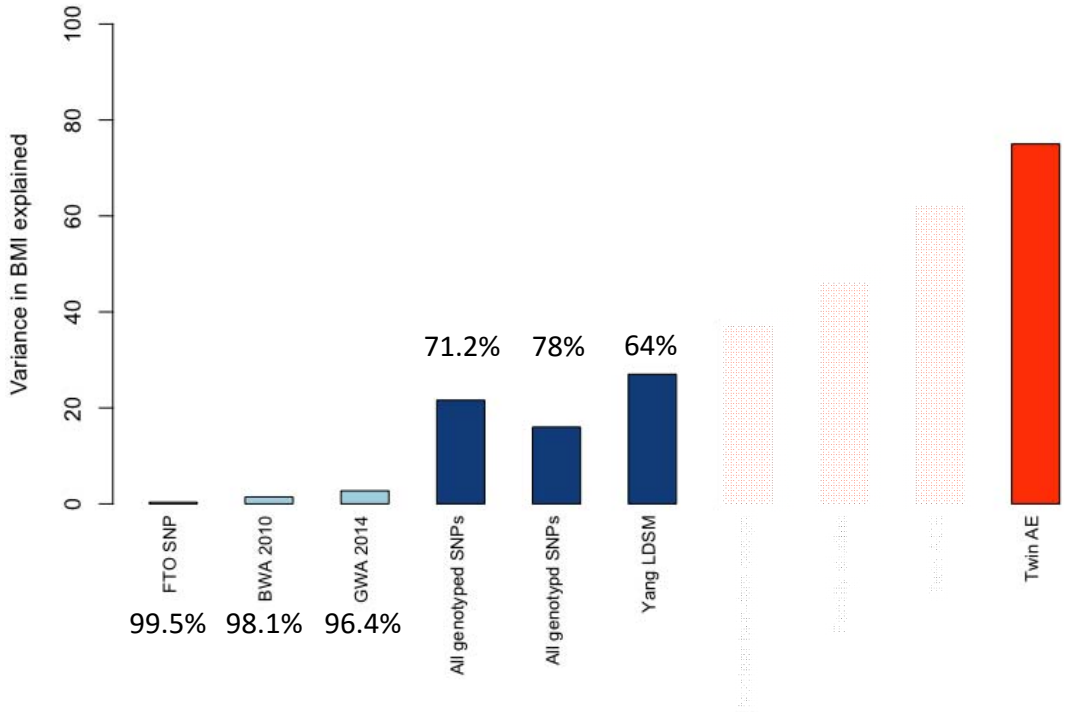

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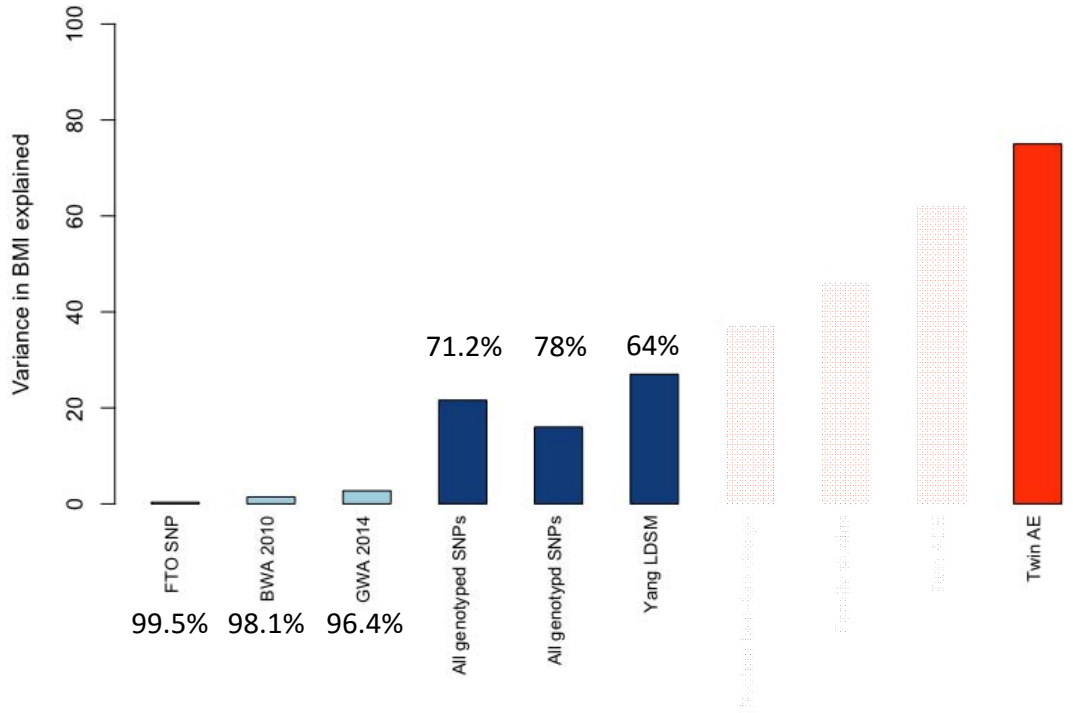
Hypothesized causes
a) Rare genetic variation
b) Overestimation of additive variance in twin models



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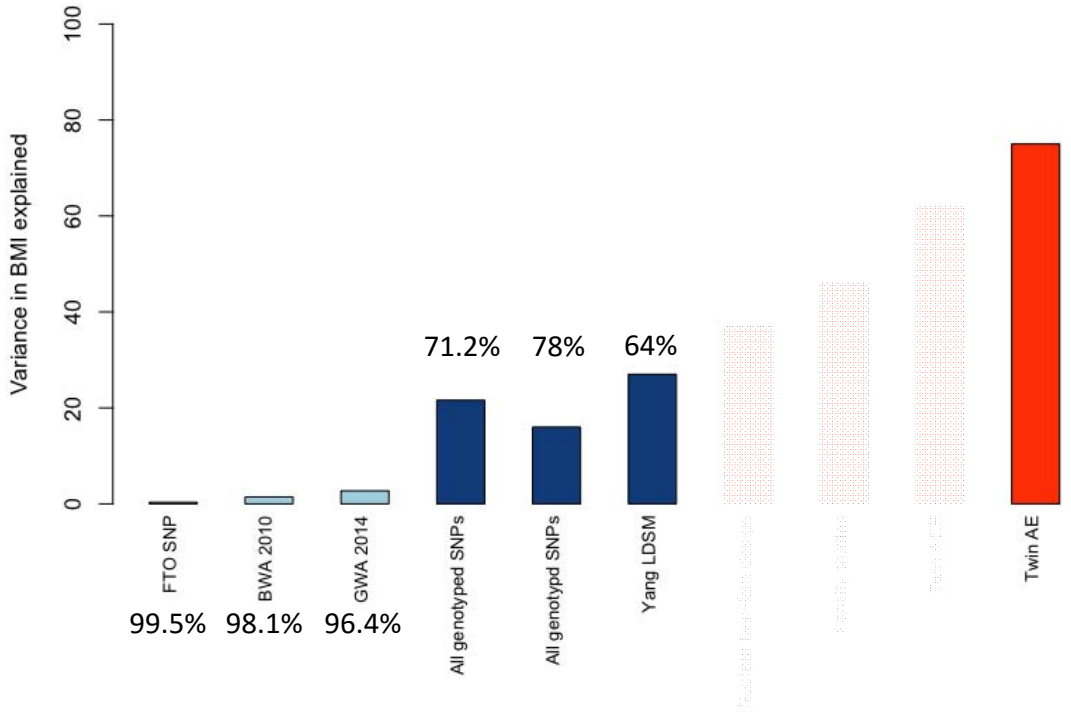
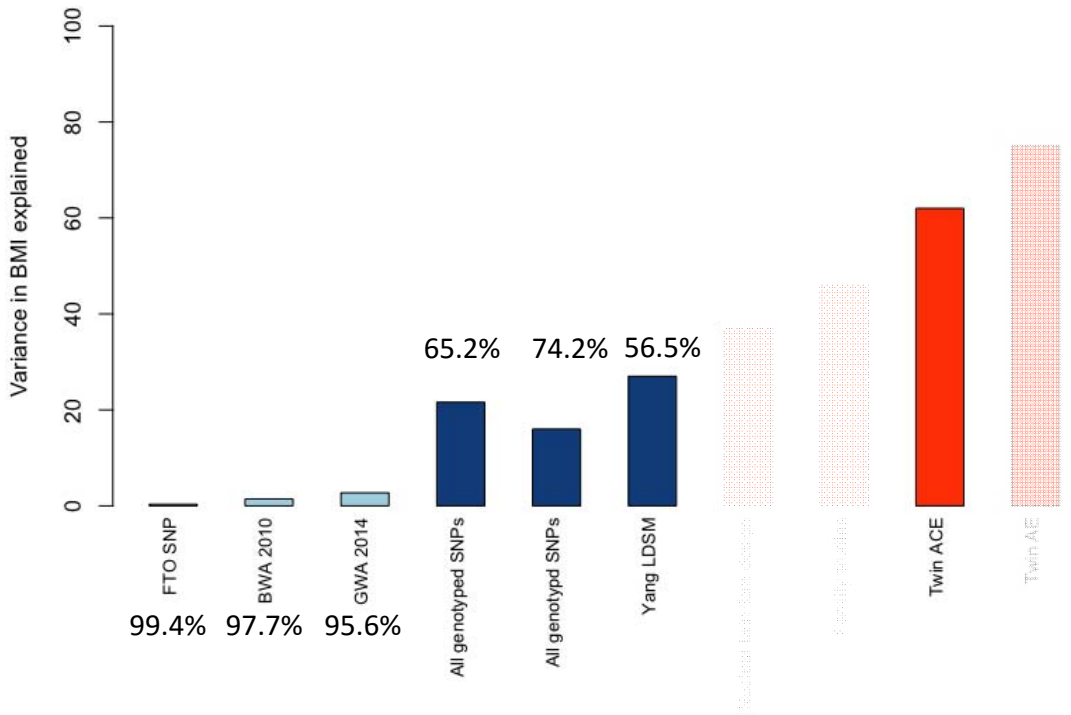


“Missing” heritability: BMI

Hypothesized causes

1. Rare genetic variation
2. **Overestimation of additive variance in twin model**
    a) **Allow for common environment**
        a) **h^2 75% -> 62%**



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1. Rare genetic variation
2. **Overestimation of additive variance in twin model**
    a) Allow for common environment
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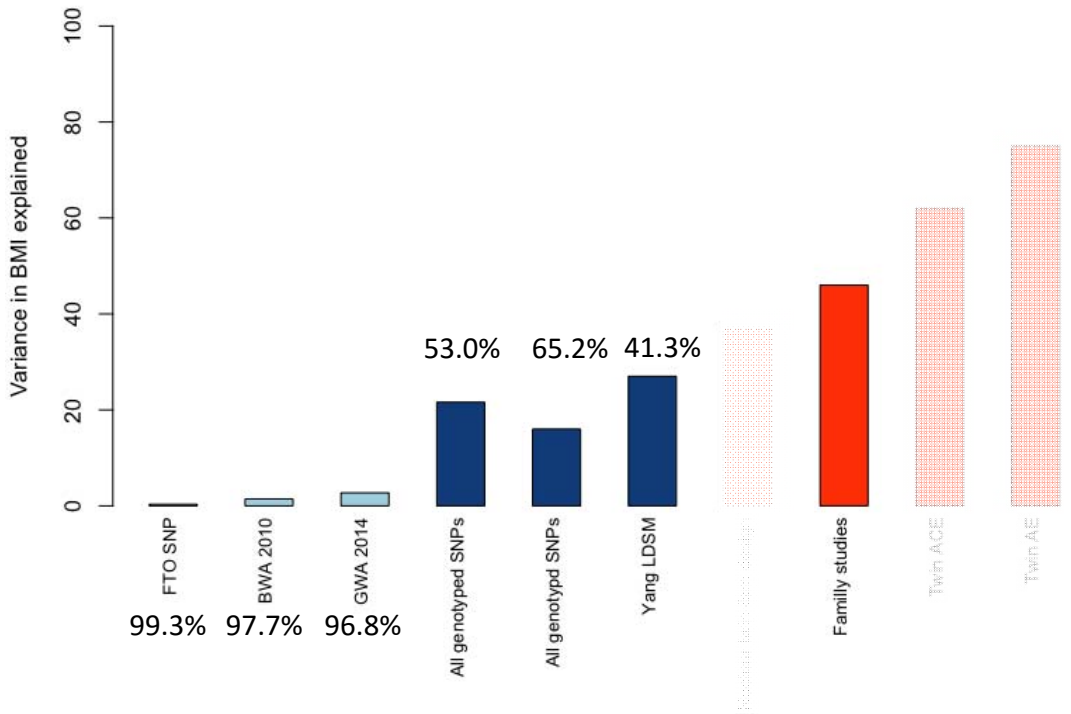
        a) h^2 75% -> 46%



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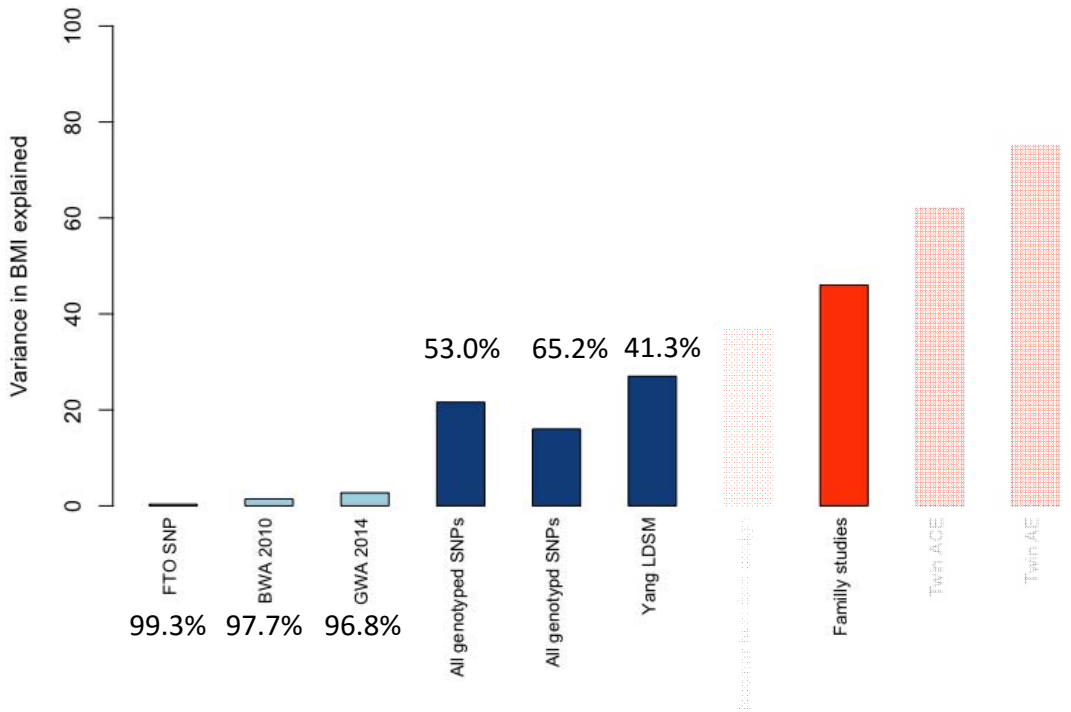
   c) Fit the Nuclear Twin-Family model



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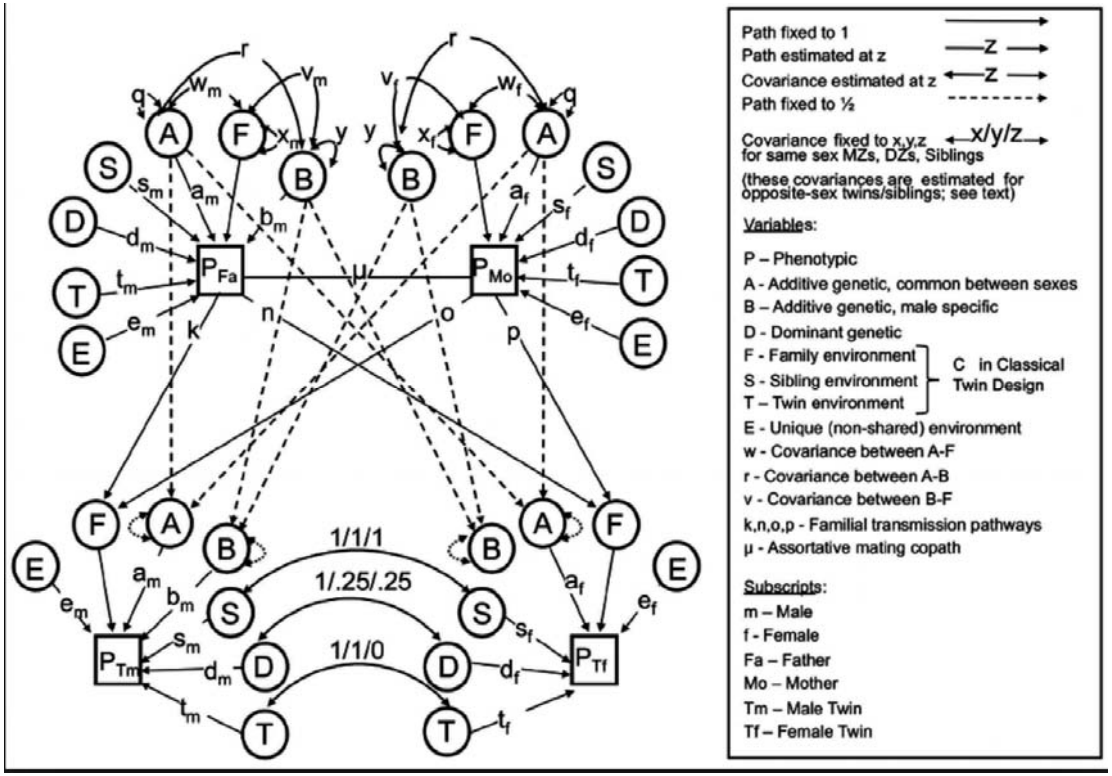
   b) **Rely on family members instead of twins**
      a) **h^2 75% -> 46%**
   c) **Fit the Nuclear Twin-Family model**
      a) **Non-random mating**
      b) **Dominance variation**
      c) **Common environment**



Maes, Eaves, Neale 1997

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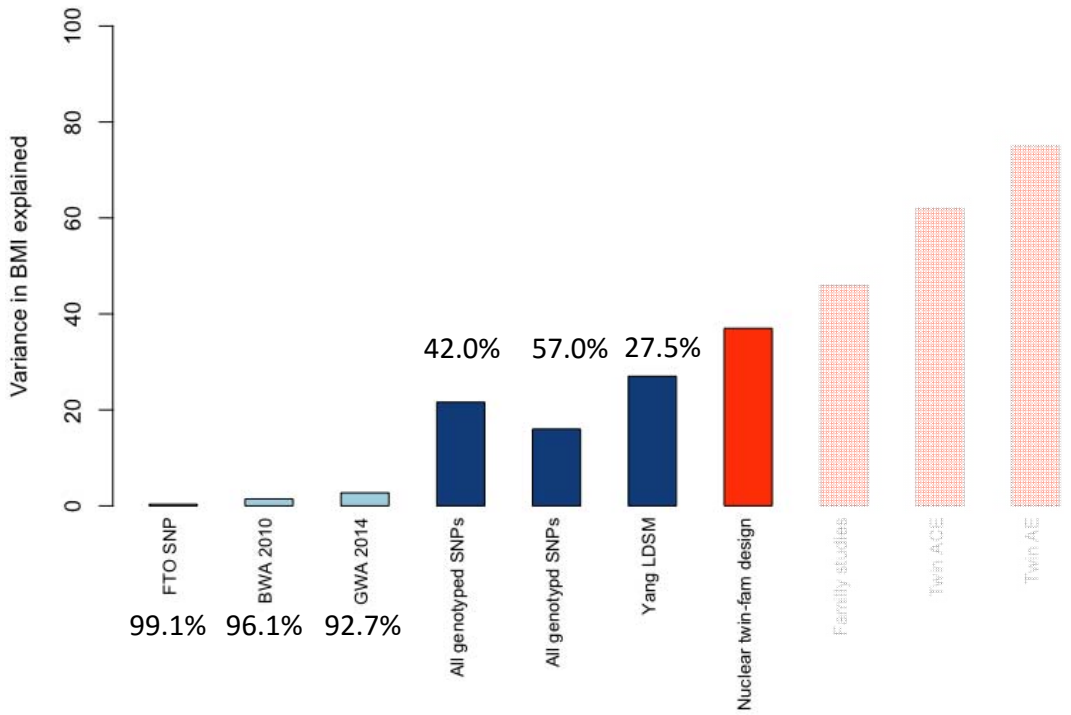
        a) h^2 75% -> ~37%



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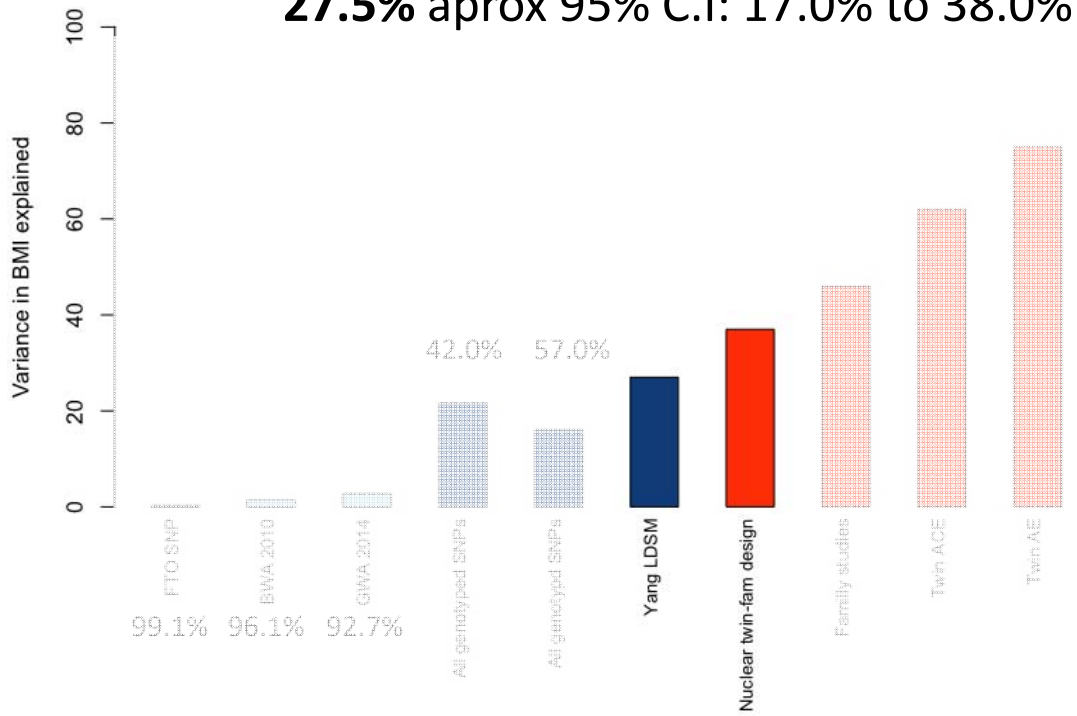
27.5% aprox 95% C.I: 17.0% to 38.0%



“Missing” heritability: BMI

27.5% aprox C.I: 17.0% to 38.0%

The ratio of the “ Best” estimate based on genotyped distantly related individuals over the “ Best” estimate form a complex twin-family

Twin model captures:

Additive genetic variation
Dominance variation
Common environment “Special twin environment”
Assortment

Twin model assumes:
Absence of GxAge interaction

GCTA captures:

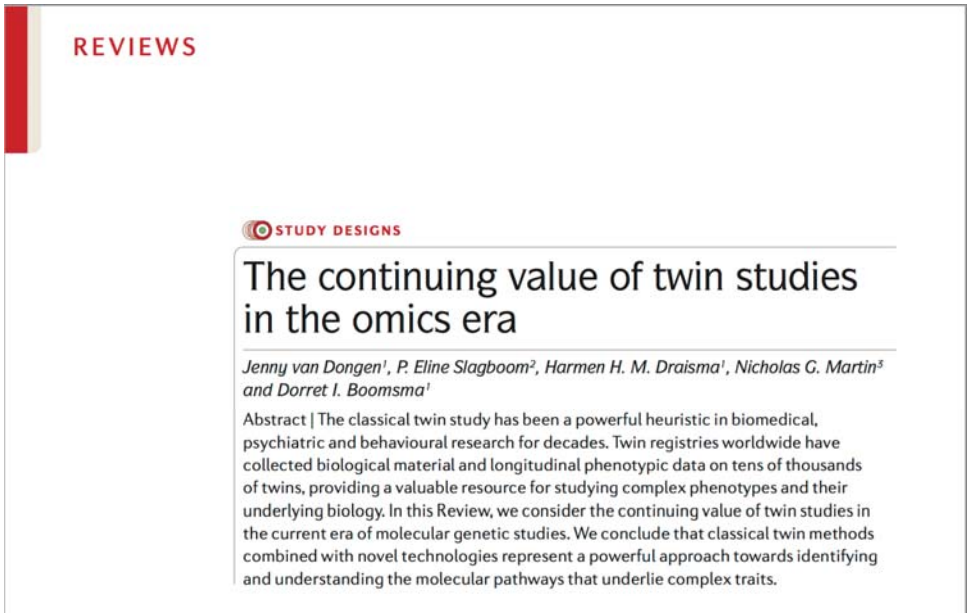
99% of common additive genetic effects, 68% of additive rare genetic effects*

GCTA assumes:

No assortment

* Yang et al 2014

The (gen)omic era: the continued relevance of twin studies.



REVIEWS

STUDY DESIGNS

The continuing value of twin studies in the omics era

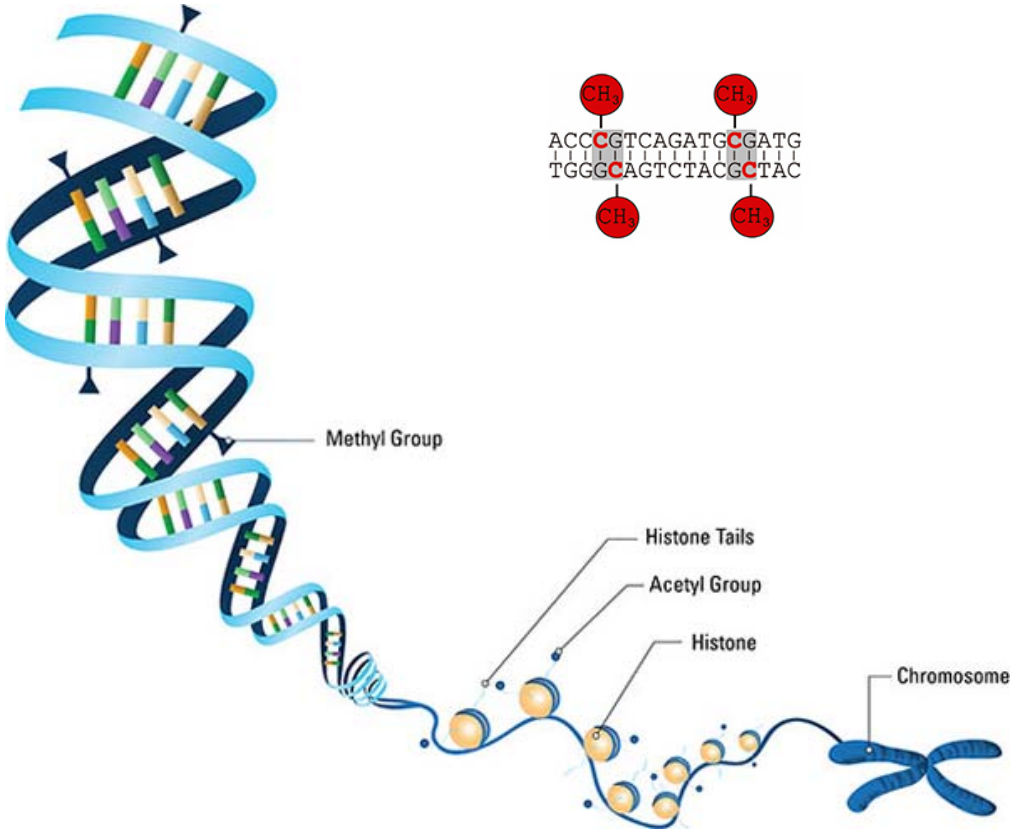
Jenny van Dongen[1], P. Eline Slagboom[2], Harmen H. M. Draisma[1], Nicholas G. Martin[3] and Dorret I. Boomsma[1]

Abstract | The classical twin study has been a powerful heuristic in biomedical, psychiatric and behavioural research for decades. Twin registries worldwide have collected biological material and longitudinal phenotypic data on tens of thousands of twins, providing a valuable resource for studying complex phenotypes and their underlying biology. In this Review, we consider the continuing value of twin studies in the current era of molecular genetic studies. We conclude that classical twin methods combined with novel technologies represent a powerful approach towards identifying and understanding the molecular pathways that underlie complex traits.

Van Dongen, J., Slagboom, P. E., Draisma, H. H., Martin, N. G., & Boomsma, D. I. (2012). The continuing value of twin studies in the omics era. *Nature Reviews Genetics*, *13*(9), 640-653.

Epigenetic variation

CpG methylation can vary across the lifespan



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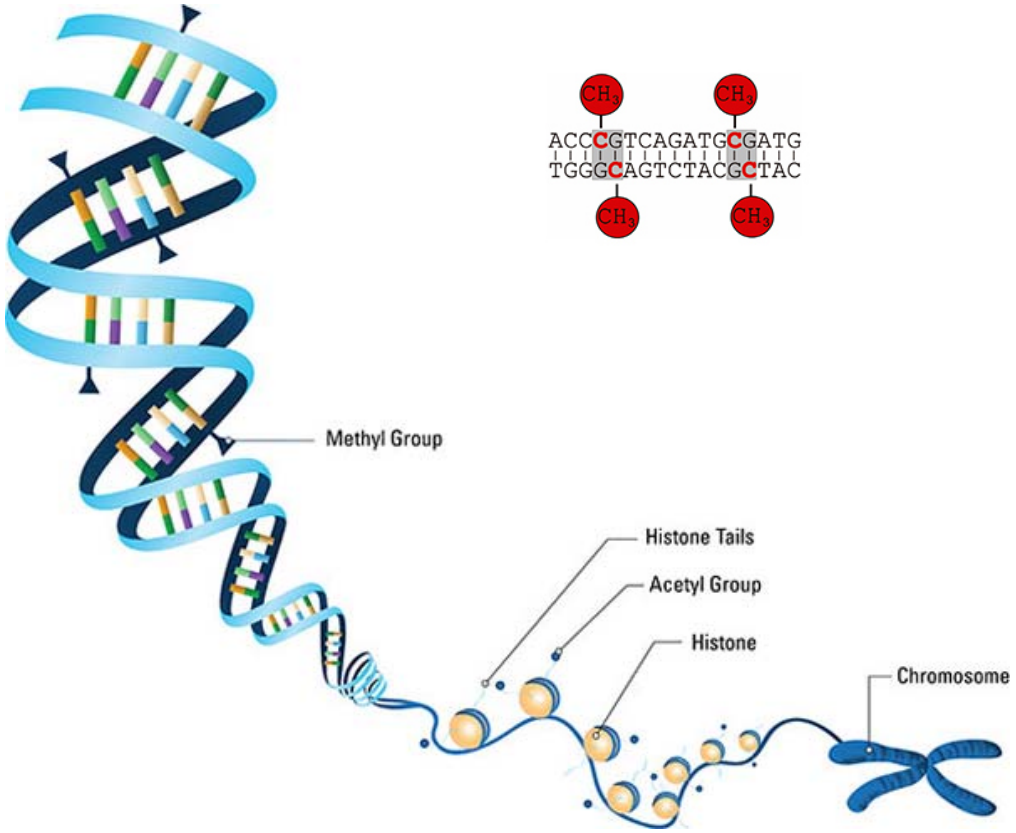

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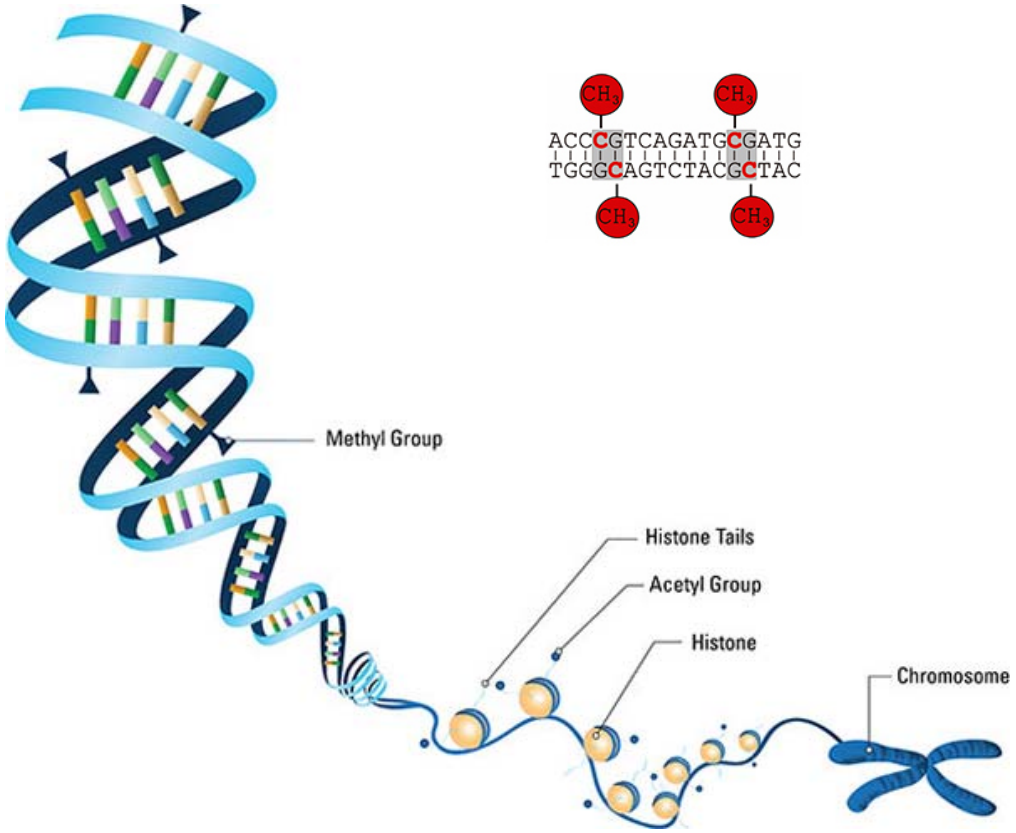

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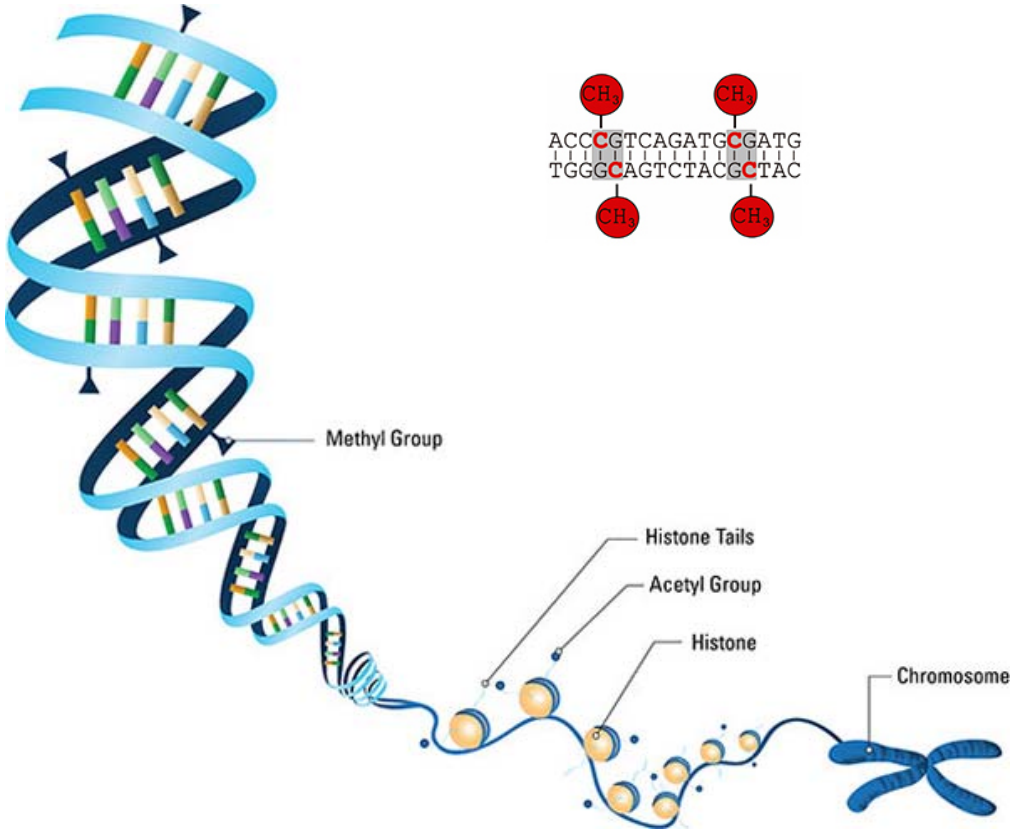
CpG methylation can vary across tissues

CpG methylation changes the expression of genes

Epigenetic variation



CpG methylation can vary across the lifespan

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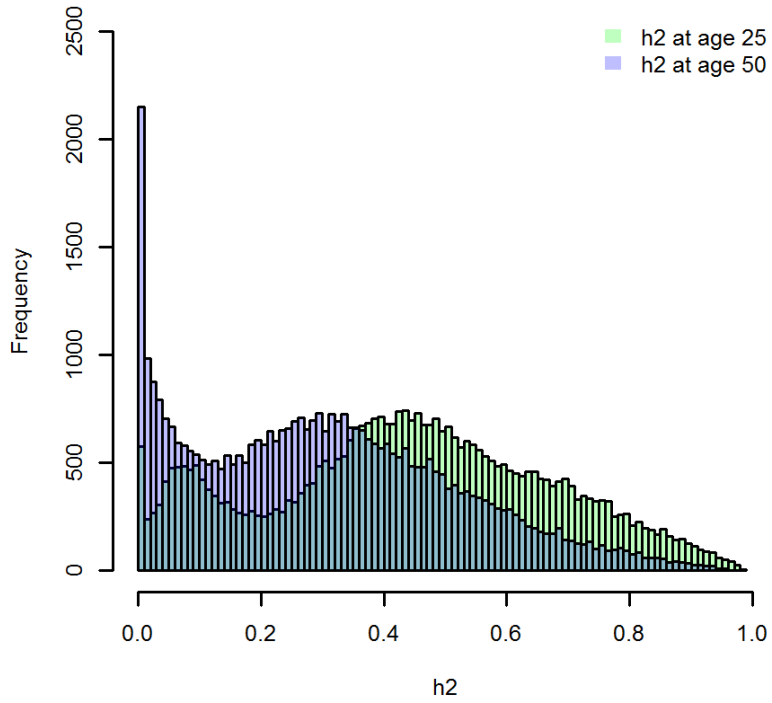
CpG methylation changes the expression of genes

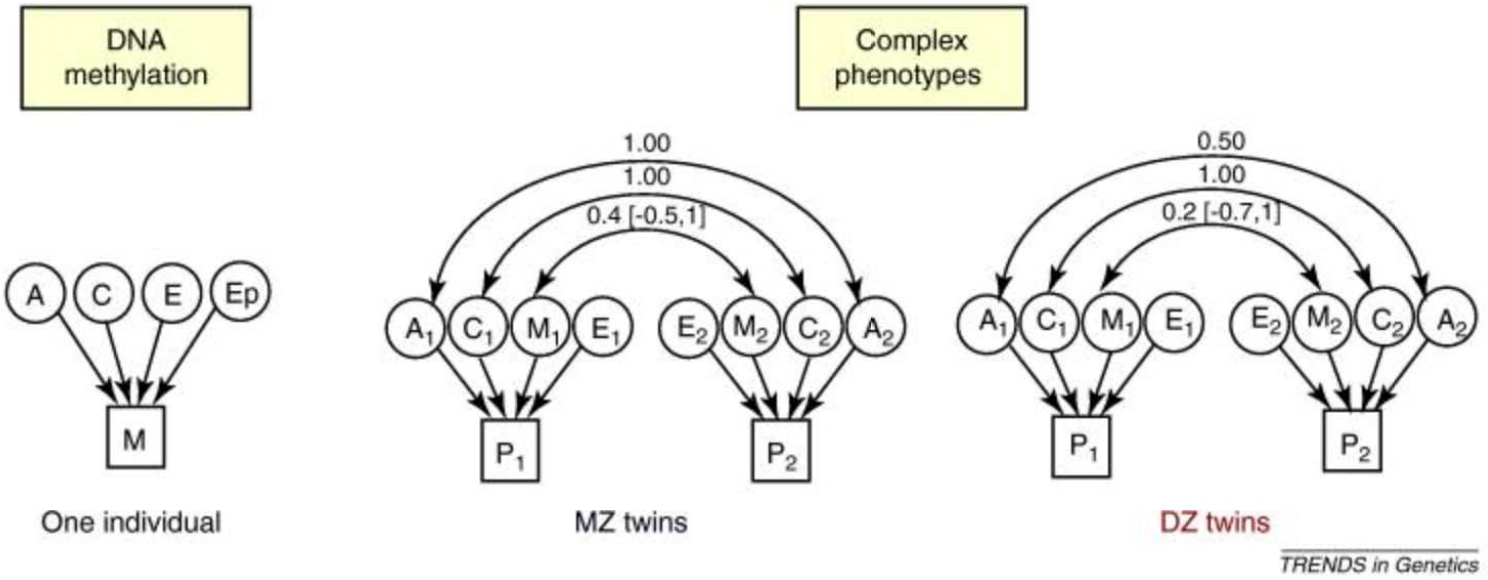
CpG Methylation is **NOT** identical in MZ twins, and does **NOT** correlate .5 between DZ twins

Heritability of CpG methylation



Van Dongen et al. 2016

CpG Methylation in the twin model



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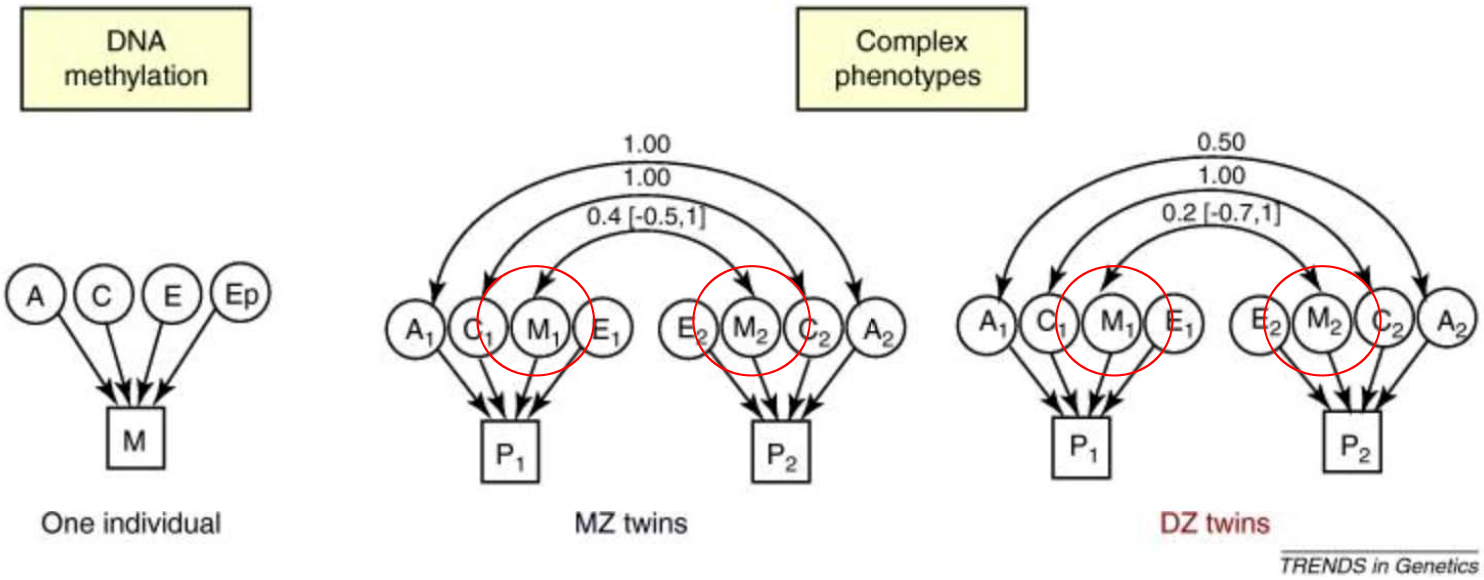

Bell & Spector (2011)

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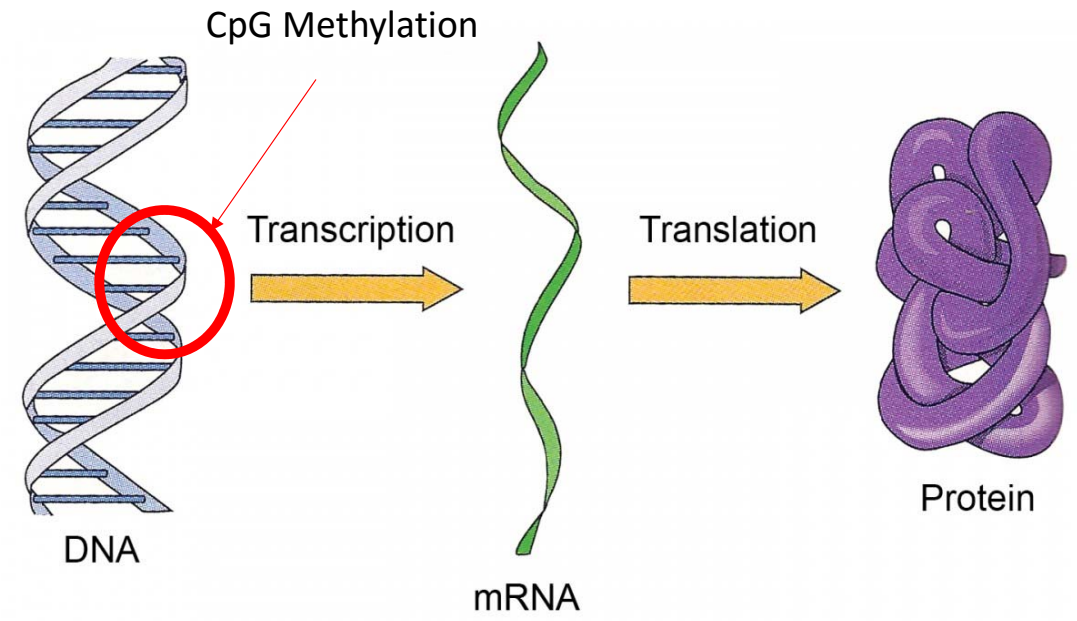

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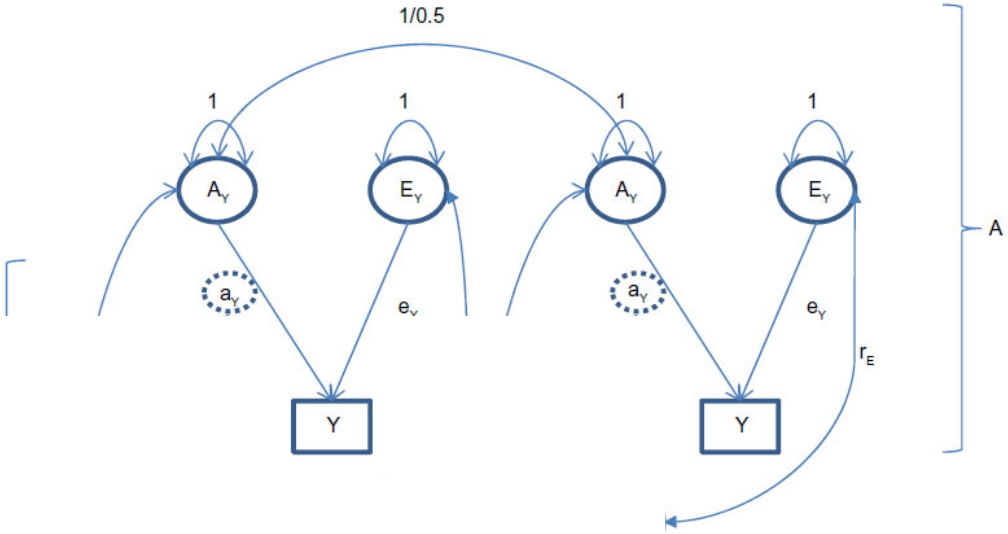

Dolan et al. 2015

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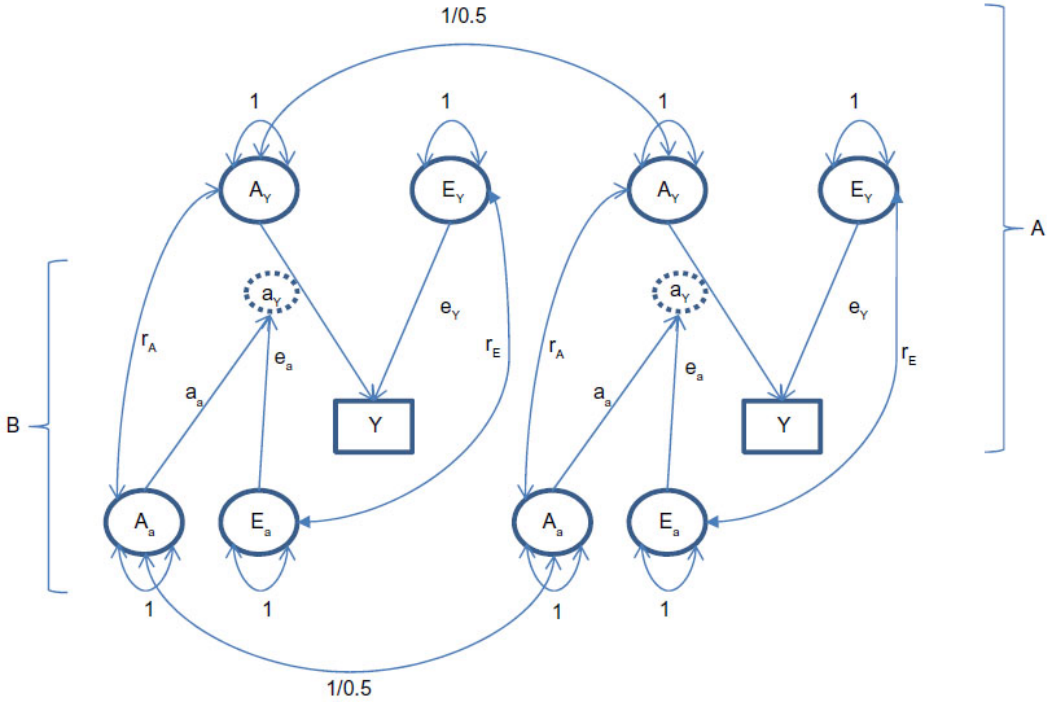

Dolan et al. 2015

CpG Methylation in the twin model: Caveats

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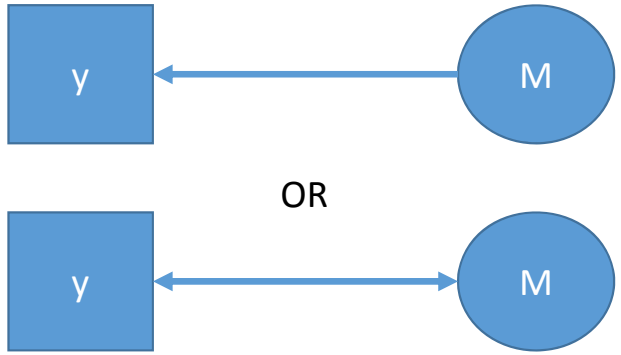

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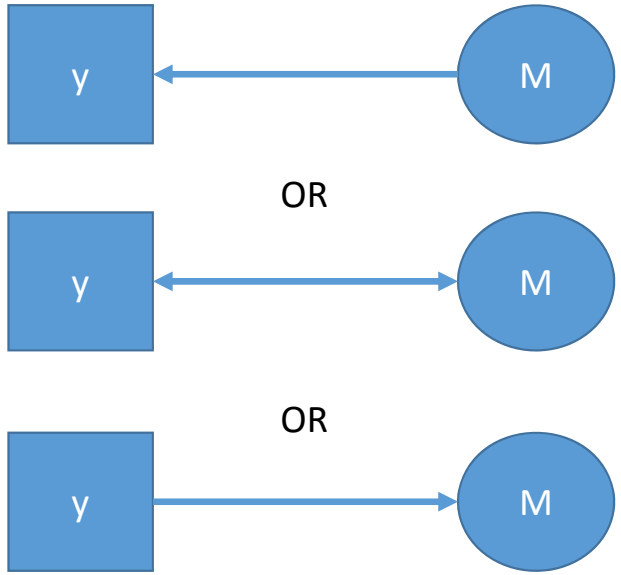

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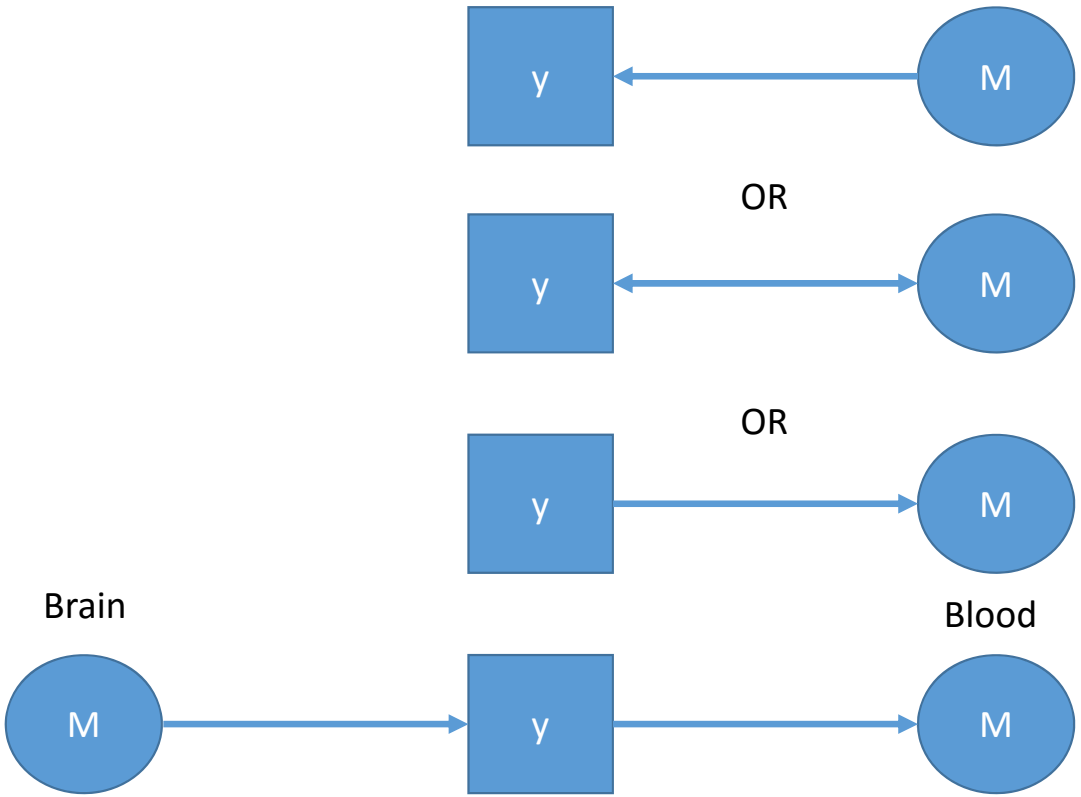

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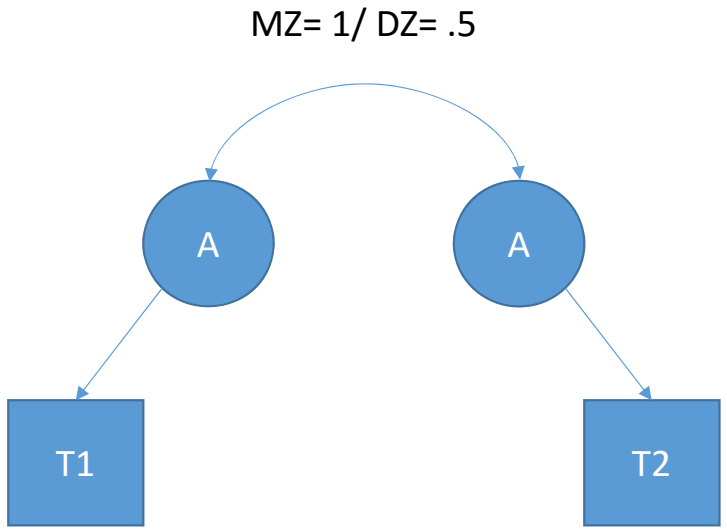

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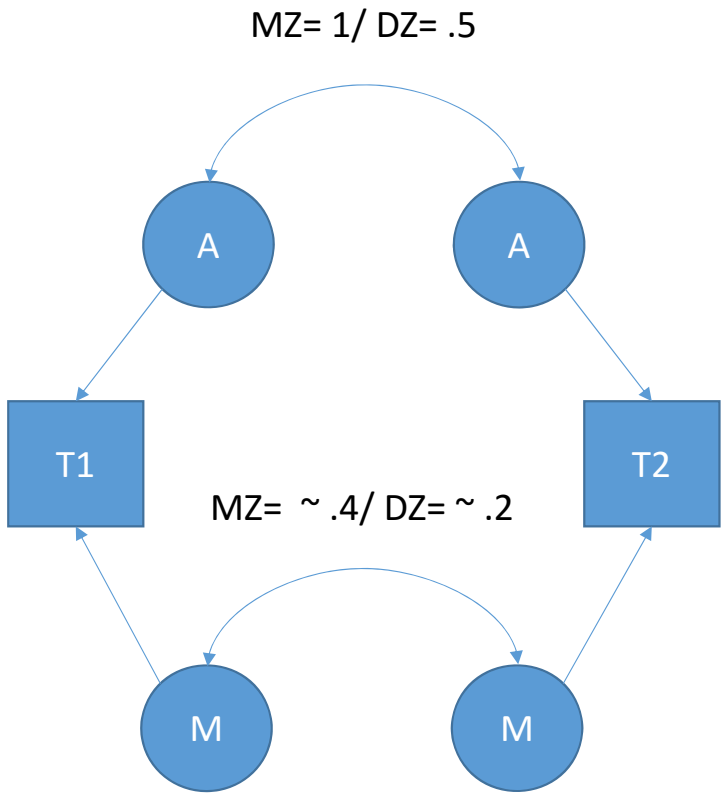
3. Methylation varies over time



CpG Methylation in the twin model: Caveats

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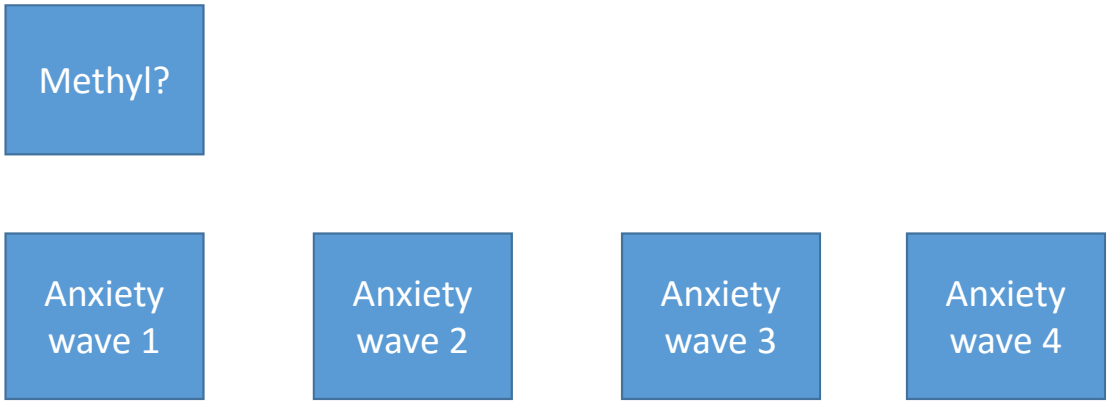

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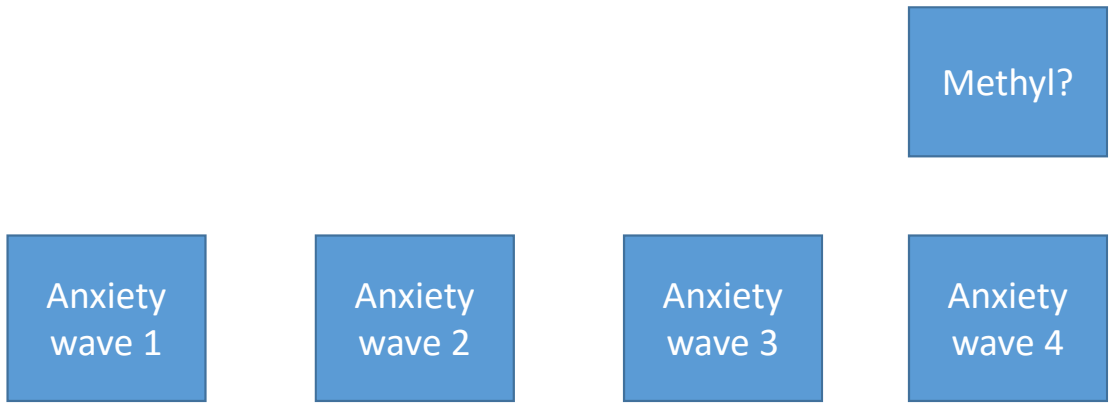

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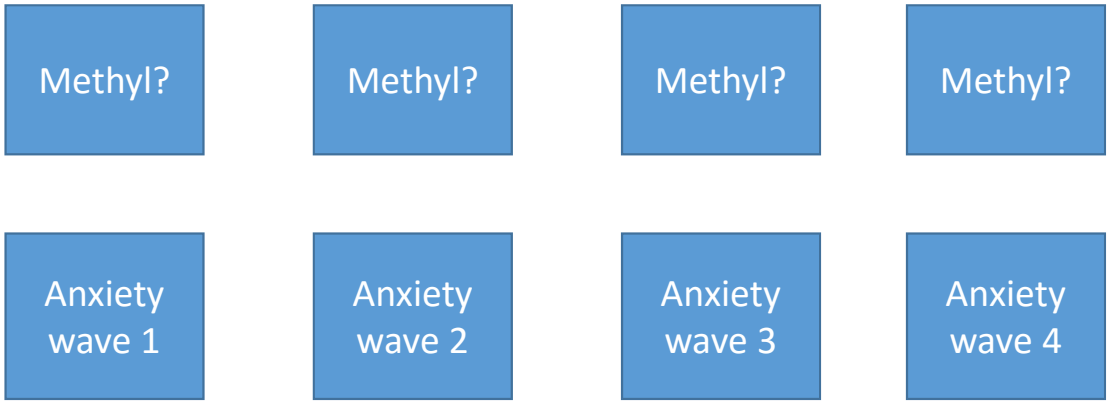
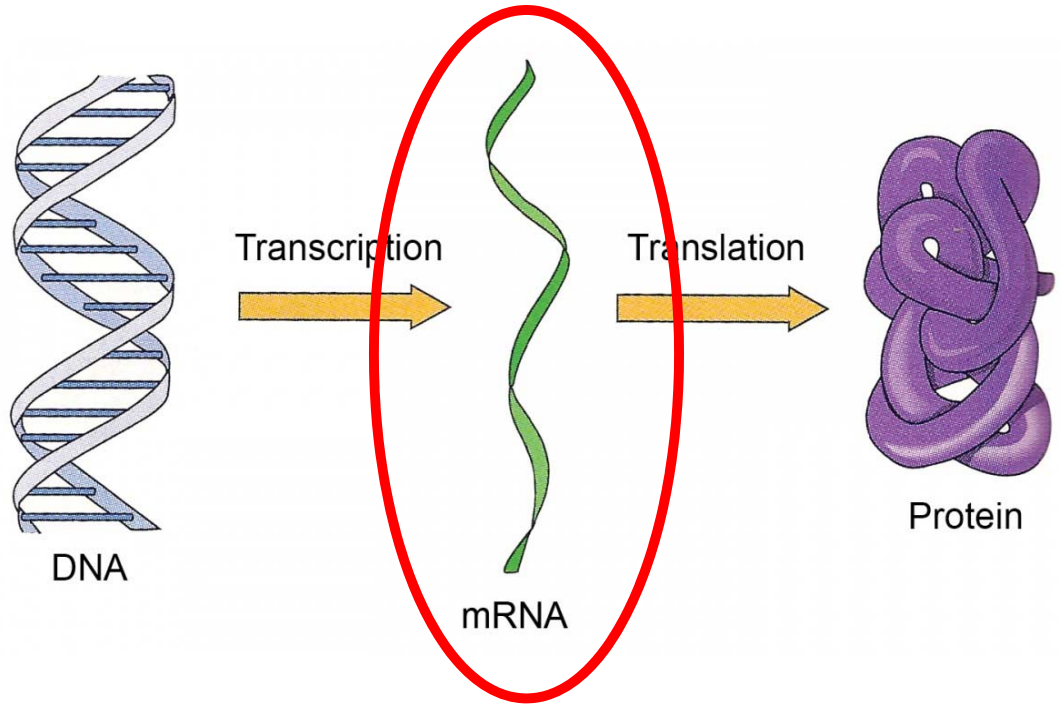
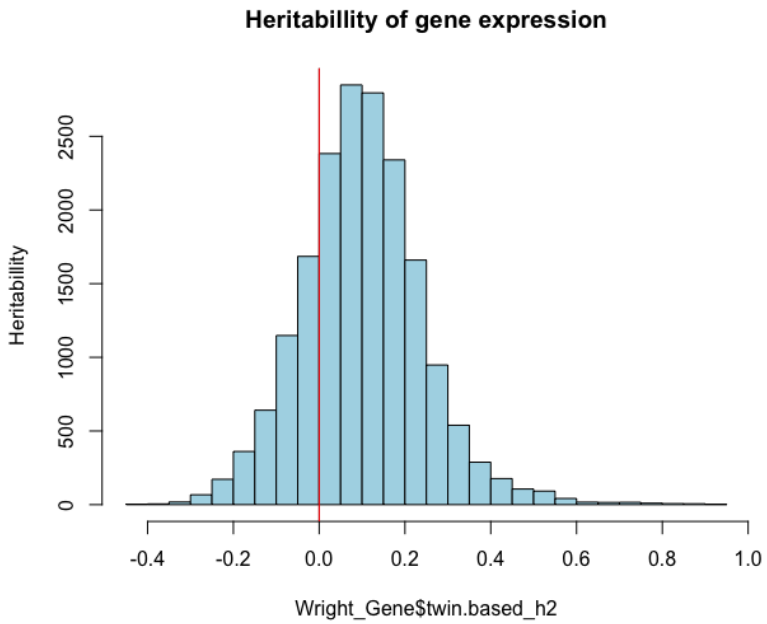


The next step: Gene expression



Heritability of gene expression



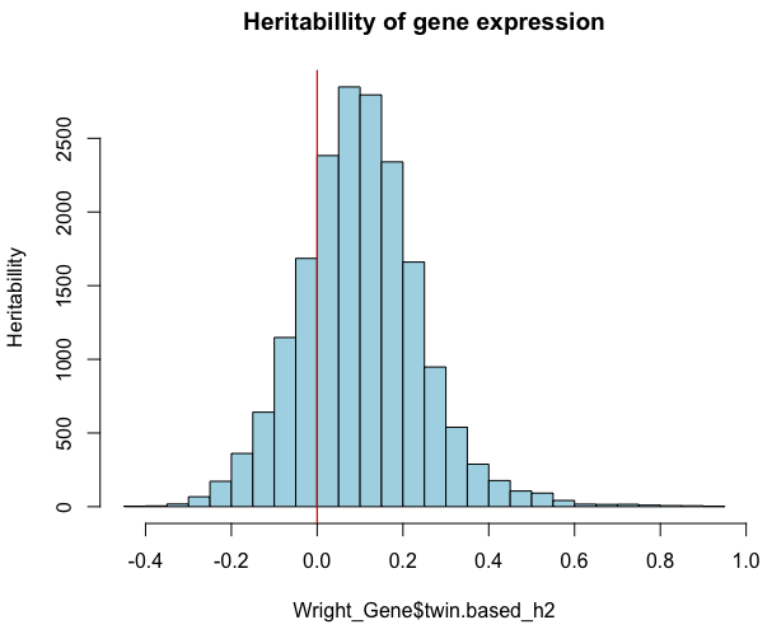
Wright et al. (2014):

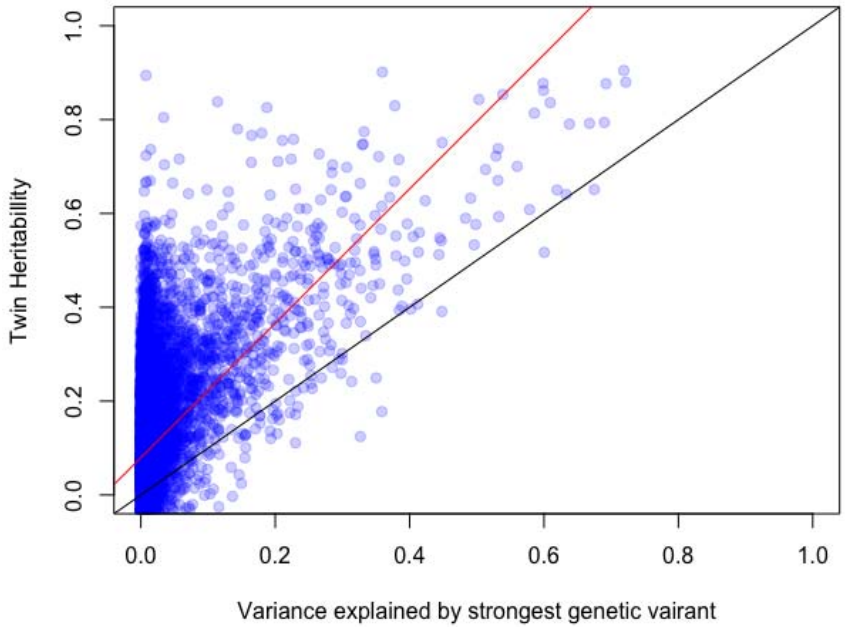
Assessed gene expression profiles in 2,752 twins

Assessedd the relationship between Gene expression and DNA sequence

Wright, F. A., Sullivan, P. F., Brooks, A. I., Zou, F., Sun, W., Xia, K., ... & Abdellaoui, A. (2014). Heritability and genomics of gene expression in peripheral blood. *Nature genetics*, *46*(5), 430-437.

Heritability of gene expression





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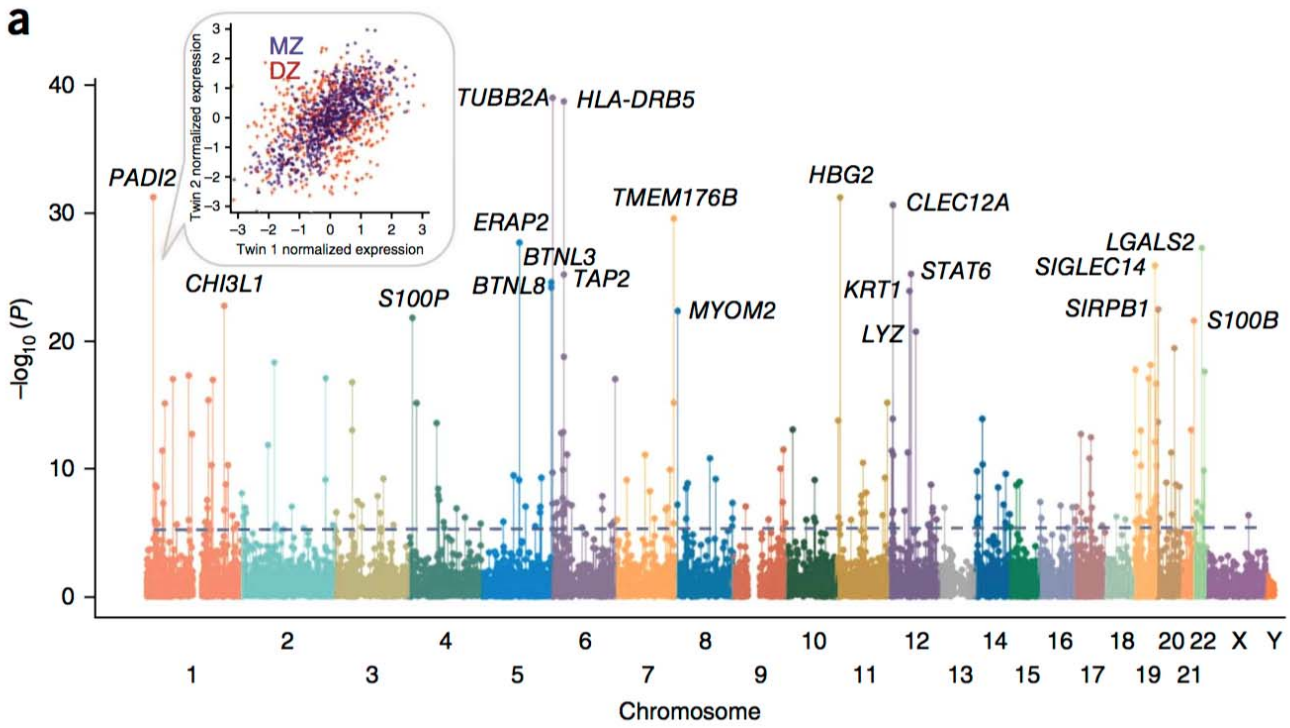

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GC content, –5 kb of TSS		–0.72	0.471	**–5.00**	**5.73×10^{-7}**
DHS near TSS[a]		**9.45**	**3.55×10^{-21}**	**4.01**	**6.00×10^{-5}**
DHS near TSS, blood		**8.87**	**7.02×10^{-16}**	1.30	0.195
Gene density[b]		**–6.98**	**2.98×10^{-12}**	**–10.85**	**2.09×10^{-27}**
Gene size[c]		**8.07**	**7.02×10^{-16}**	**11.30**	**1.27×10^{-29}**
Local recombination rate[d]		0.73	0.464	3.01	0.0026
Size of LD block[e]		–0.05	0.959	–0.49	0.622
Gene conservation score[f]		**8.49**	**2.00×10^{-17}**	1.14	0.255
Genes under selection (185)[g]	0.013	1.60	0.109	1.82	0.068
Genes under positive selection (549)[h]	0.007	1.32	0.186	1.78	0.074
Genes under balancing selection (47)[i]	0.042	2.65	0.0081	2.83	0.0046
Genes under adaptive selection (174)[j]	0.019	2.26	0.024	1.13	0.260
Human accelerated genes (161)[k]	0.024	3.05	0.0023	**4.12**	**3.73×10^{-5}**
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NHGRI GWAS catalog (2,343)[l]	**0.018**	**7.42**	**1.14×10^{-13}**	**7.52**	**5.53×10^{-14}**
NHGRI, chr. 6 genes removed (2,142)	**0.016**	**6.06**	**1.37×10^{-9}**	**6.42**	**1.36×10^{-10}**
NHGRI, immune diseases (720)[m]	**0.032**	**7.22**	**5.02×10^{-13}**	**5.77**	**7.99×10^{-9}**
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OMIM disease entries (3,089)[n]	**0.018**	**8.87**	**7.63×10^{-19}**	**7.54**	**4.81×10^{-14}**
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Not all genes are equally heritable!

Wright, F. A. et al (2014)

Heritability of gene expression

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Genes near regions that can be epigenetically Modified, are less heritable.

Wright, F. A. et al (2014)

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Large genes are more heritable, Genes in gene dense regions are less heritable.

Wright, F. A. et al (2014)

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Genes associate to disease, and near genome wide Signals for complex traits show increased heritability

Wright, F. A. et al (2014)

How can all of this help your research?

- Tissue Gene expression:
- http://www.gtexportal.org/home/

- Developmental transcriptome:
- http://www.brainspan.org/rnaseq/search/index.html

- Developmental epigenome:
- http://www.brainspan.org/static/download.html

Genetic epidemiology in the genomic age: Missing Heritability & The Role of Twin Studies in the Genomic Era

- The twin study has continued use in the (gen)omic era.

- Missing heritability seems not to be a massive problem.