Epigenetics

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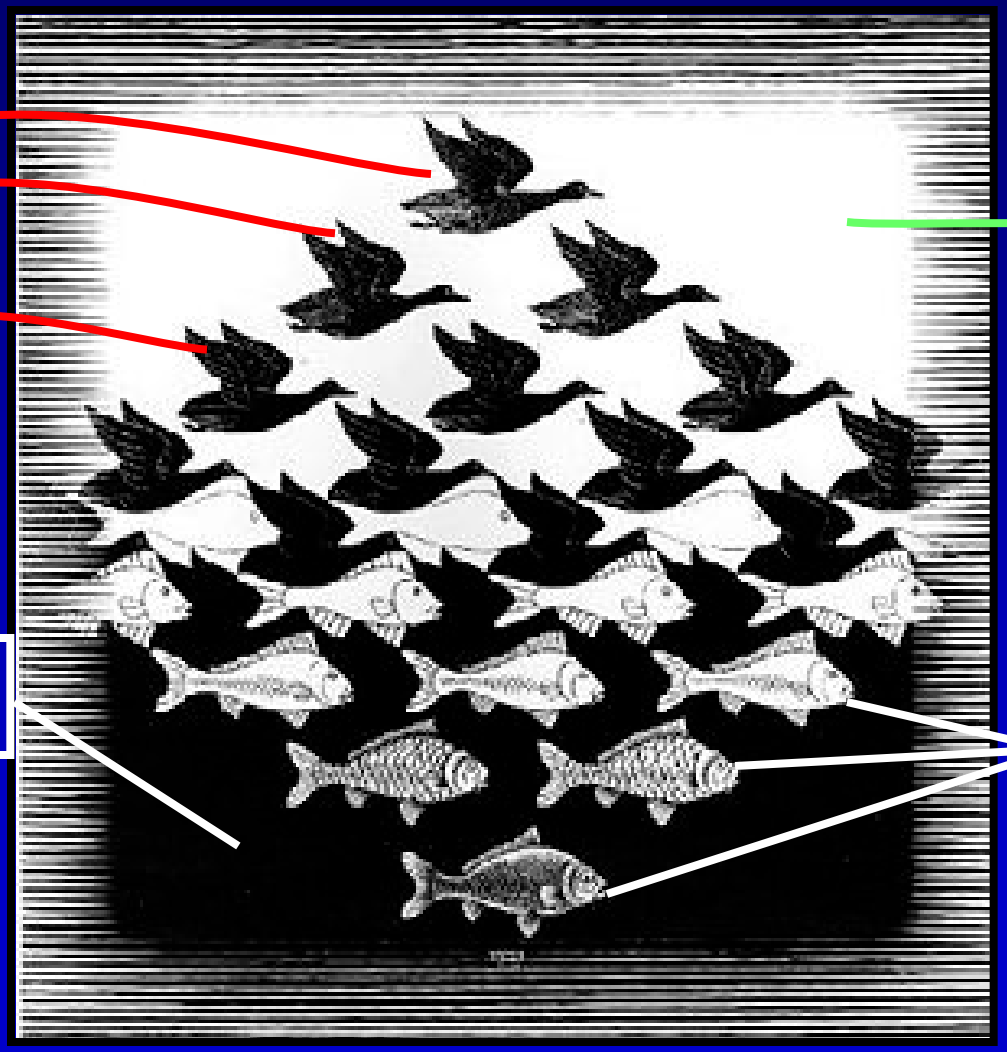
Epigenetics – a new Gestalt for etiological studies of complex diseases and traits

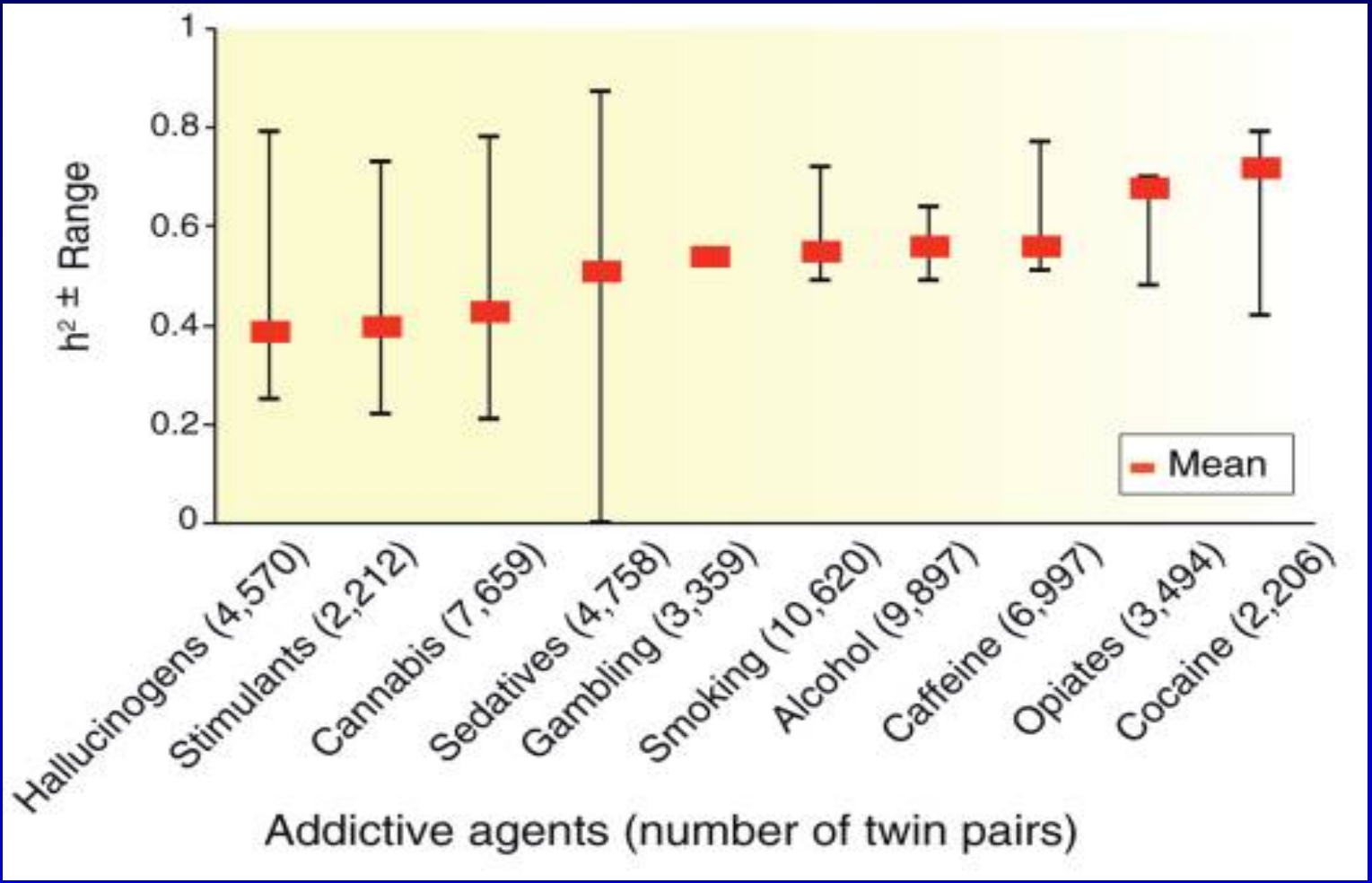


Epigenetics

Genes (DNA)+ Environment

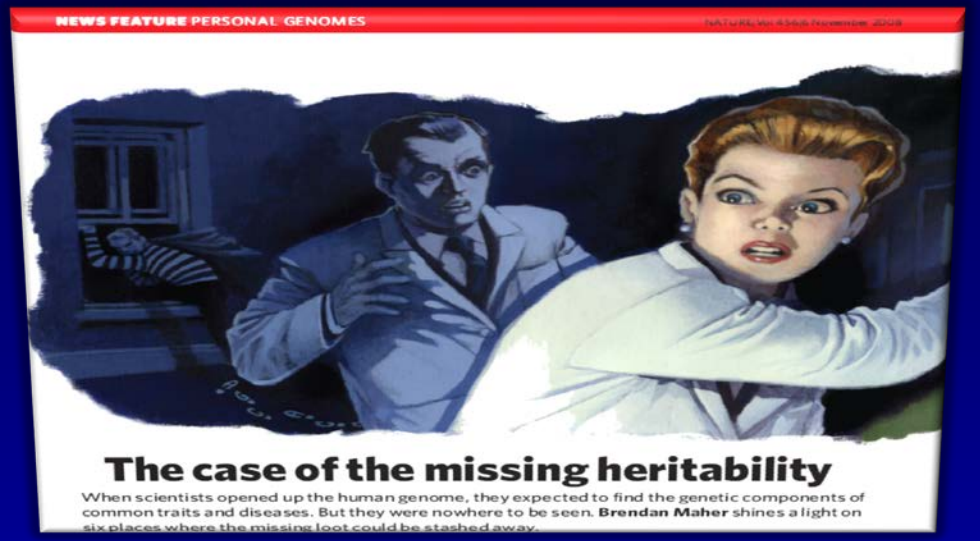
M.C. Escher

Addictions – complex disease with strong inherited predisposition



Bevilacqua and Goldman Clin Pharmacol Ther. 2009

Genetic studies: unexplained heritability



Hints of hidden heritability in GWAS

Greg Gibson

Although susceptibility loci identified through genome-wide association studies (GWAS) typically explain only a small proportion of the heritability, a classical quantitative genetic analysis now argues that considering together all common SNPs can explain a large proportion of the heritability of these complex traits. A related study provides recommendations for the sample sizes needed in future GWAS to identify additional susceptibility loci.

The mystery of missing heritability: Genetic interactions create phantom heritability

Or Zuk[a], Eliana Hechter[a], Shamil R. Sunyaev[a,b], and Eric S. Lander[a,1]

Broad Institute of MIT and Harvard, Cambridge, MA 02142; and [b]Genetics Division, Brigham and Women's Hospital, Harvard M
MA 02115

Contributed by Eric S. Lander, December 5, 2011 (sent for review October 9, 2011)

Human genetics has been haunted by the mystery of "missing heri... (frequency <1%) with large effects (3, 9)

What Environmental Factors Contribute to Addiction?

- Stress
- Early physical or sexual abuse
- Witnessing violence
- Peers who use drugs
- Drug availability

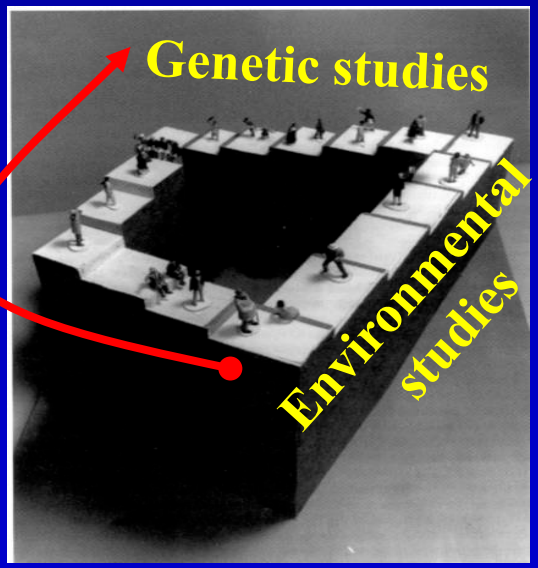
Problems in environmental studies

1. **Environmental factor and trait: cause-effect issue**

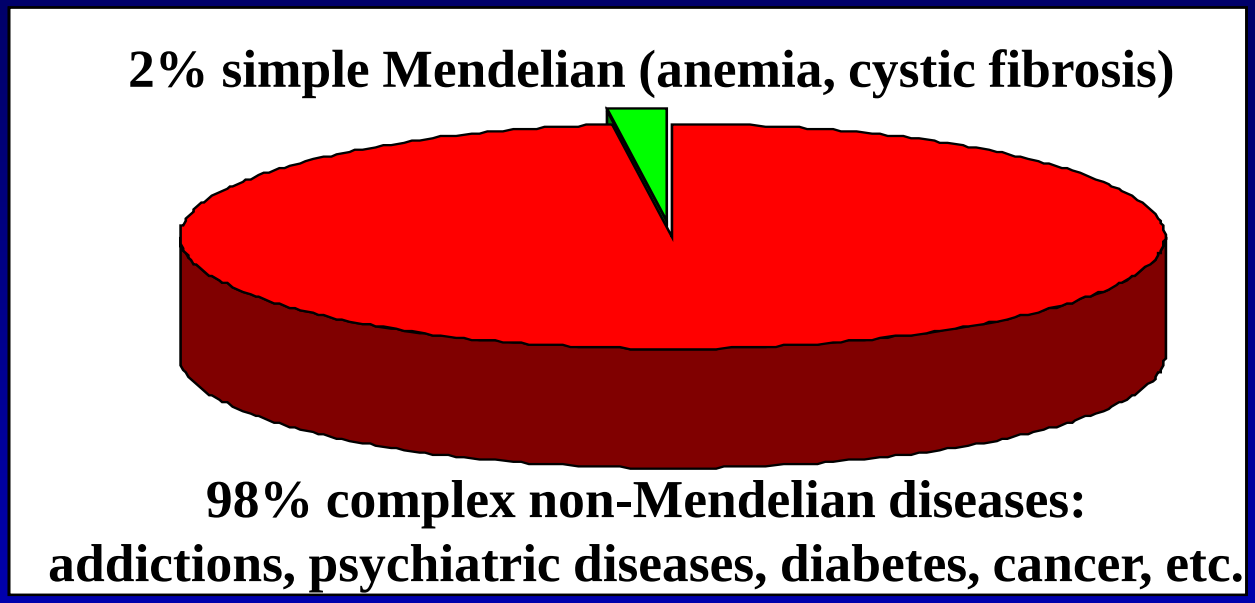
   Stressful life events → addiction

   Addiction → stressful life events

2. **Environments have their own "heritable" components, e.g. stress.** There is inherited predisposition to select themselves into high risk environments.



Genetic diseases: simple and complex



Partially heritable but do not follow Mendel's laws

Major phenotypic variability

Predominantly sporadic cases

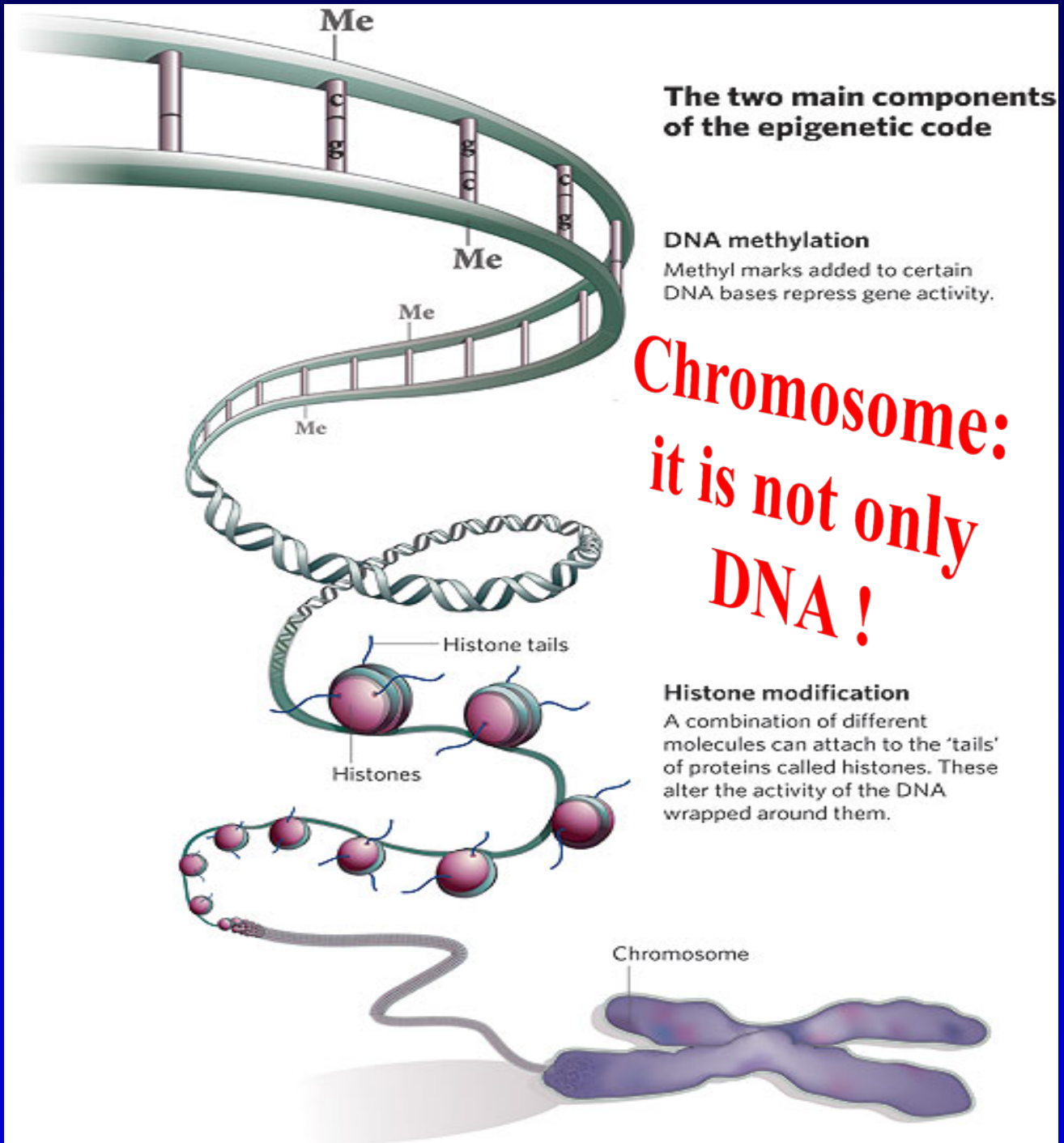
Discordance of MZ twins

Late age at onset

Parental origin effects

Sexual dimorphism

Fluctuating course



The two main components of the epigenetic code

DNA methylation

Methyl marks added to certain DNA bases repress gene activity.

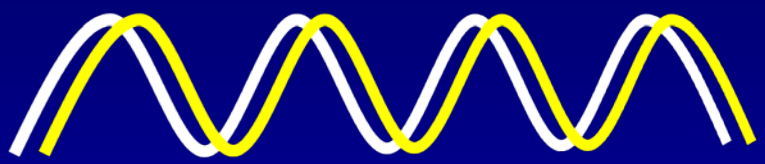
Chromosome: it is not only DNA !

Histone modification

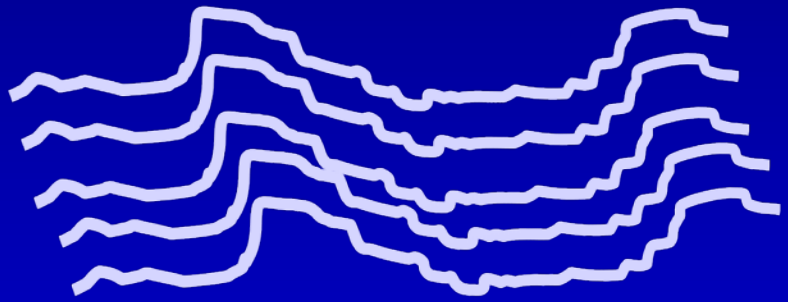
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.

Epigenetics: regulation of various genetic and genomic activities

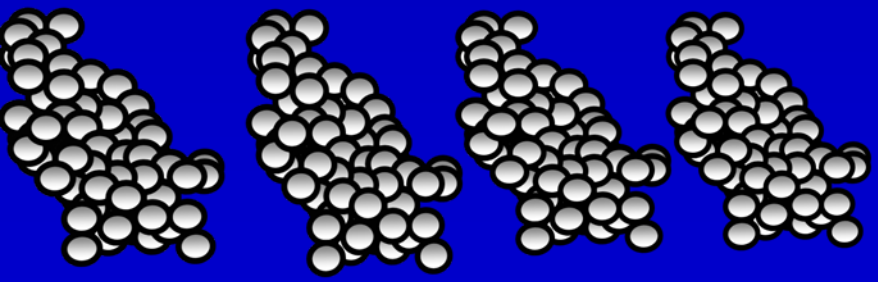
Scenario 'A'



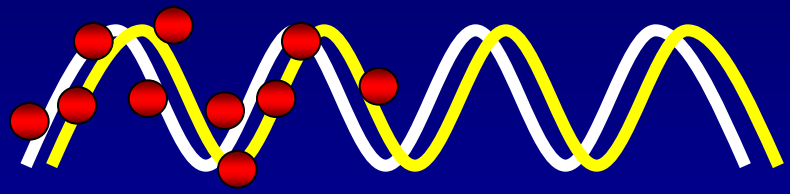
significant expression



large amounts of protein



Scenario 'B'

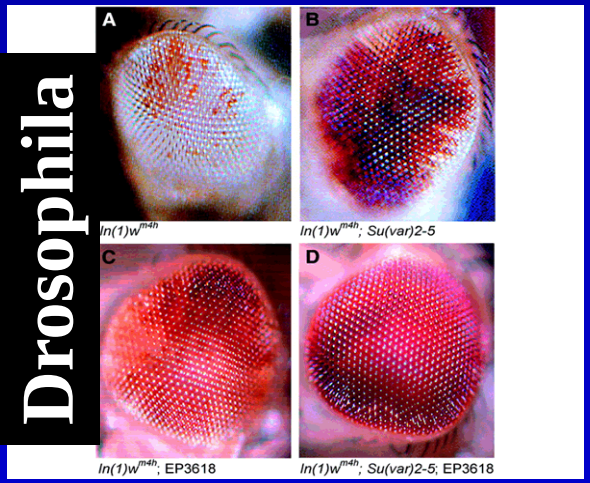


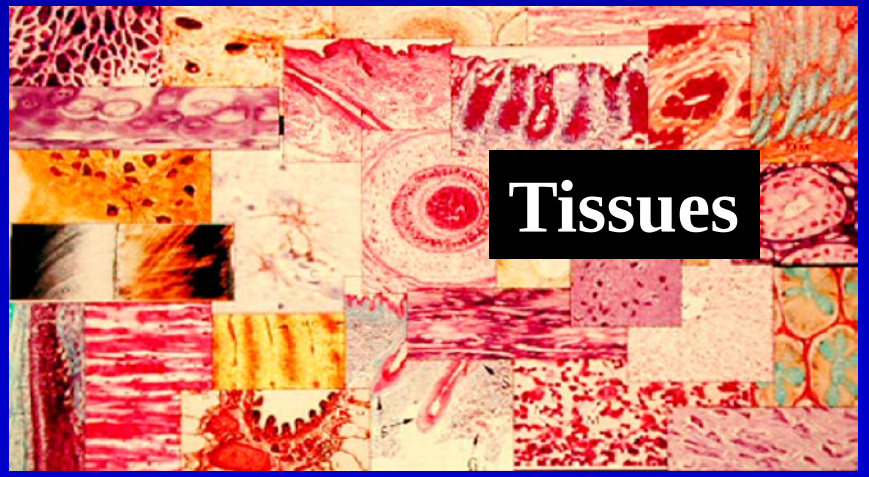
no expression

no protein

1. Epigenetics: relevance to complex disease

Epigenetic factors contribute to the phenotype





2. Epigenetics: relevance to complex disease

Like DNA, some epiG factors can be inherited

(Note: transgenerational heritability and twin-based epigenetic heritability are not the same).

PERSPECTIVES

***Nature Reviews Genetics* 2006**

OPINION

Inherited epigenetic variation — revisiting soft inheritance

Eric J. Richards

Abstract | Phenotypic variation is traditionally parsed into components that are directed by genetic and environmental variation. The line between these two

of epigenetic modifications from their genotypic context. This autonomy, coupled with the stability and persistence of epigenetic marks, provides an alternative inheritance system, operating at the interface of the familiar stable genetic system that is encoded in primary nucleotide sequence and the transient protein–DNA interactions that mediate gene-expression changes in response to developmental signals and environmental stimuli.

***Nature Reviews Genetics* 2012**

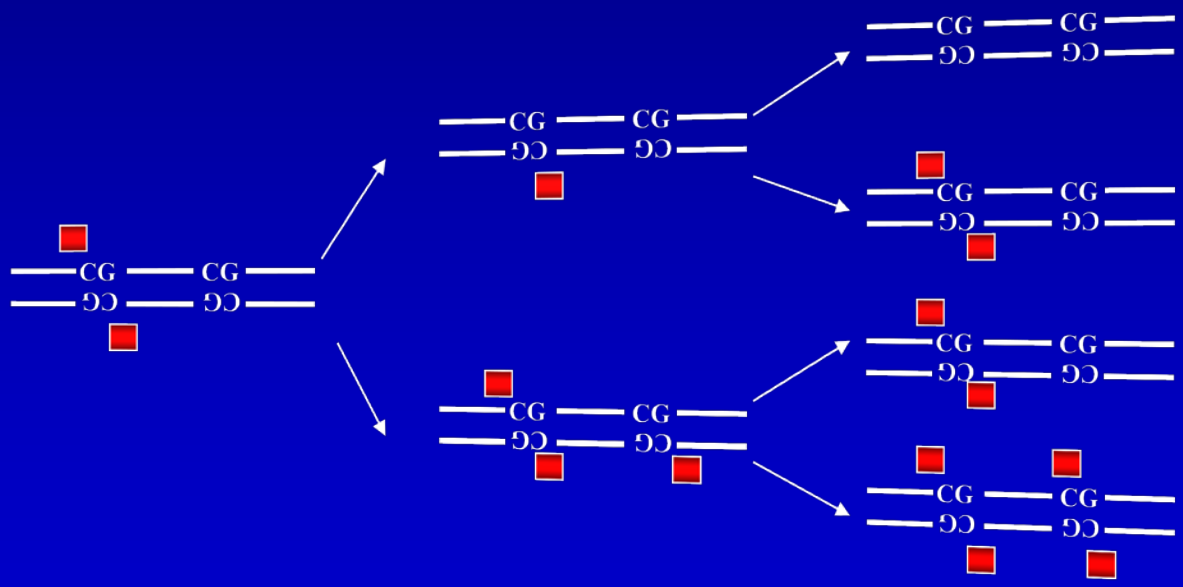
Understanding transgenerational epigenetic inheritance via the gametes in mammals

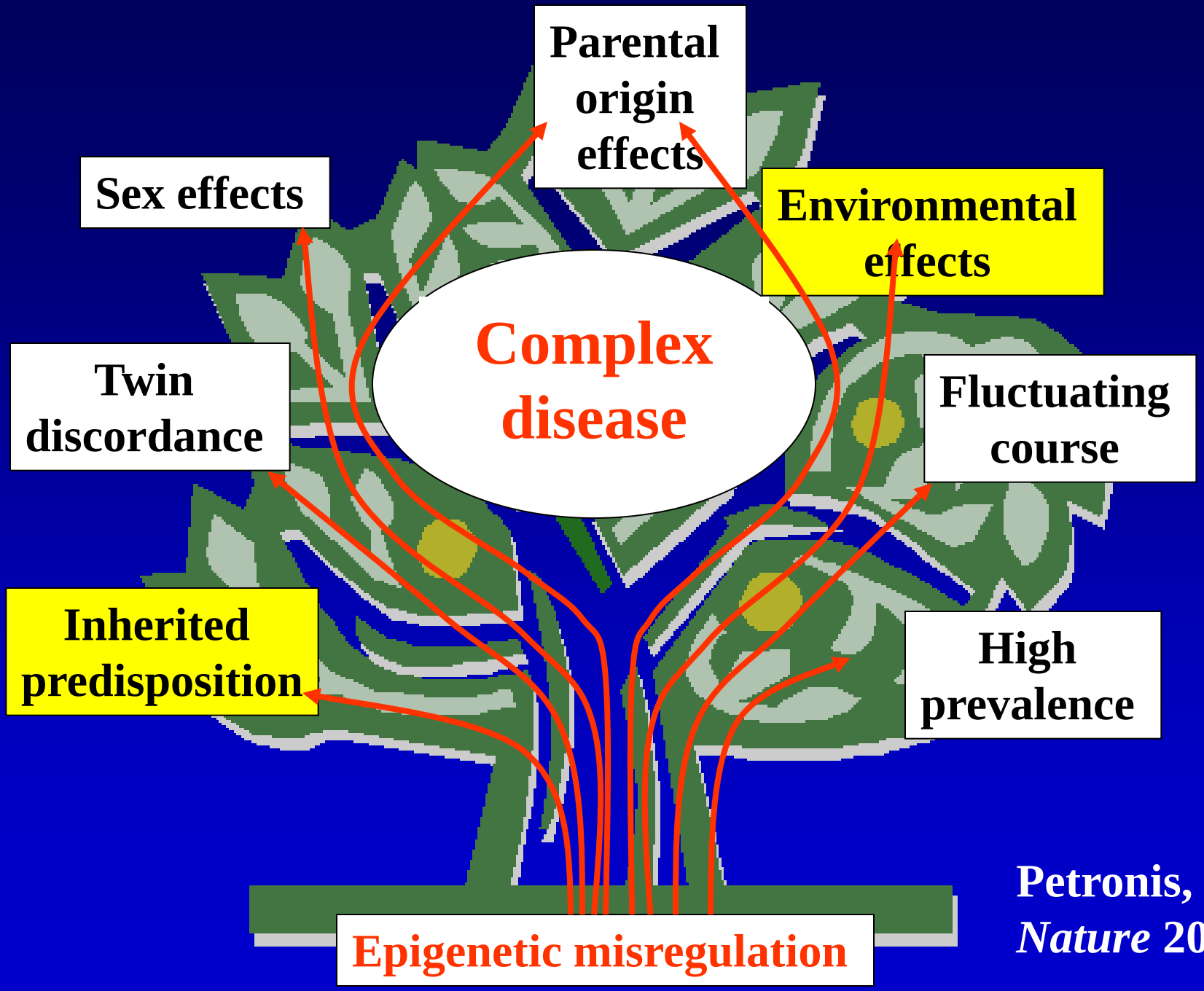
Lucia Daxinger and Emma Whitelaw

Abstract | It is known that information that is not contained in the DNA sequence — epigenetic information — can be inherited from the parent to the offspring. However, many questions remain unanswered regarding the extent and mechanisms of such inheritance.

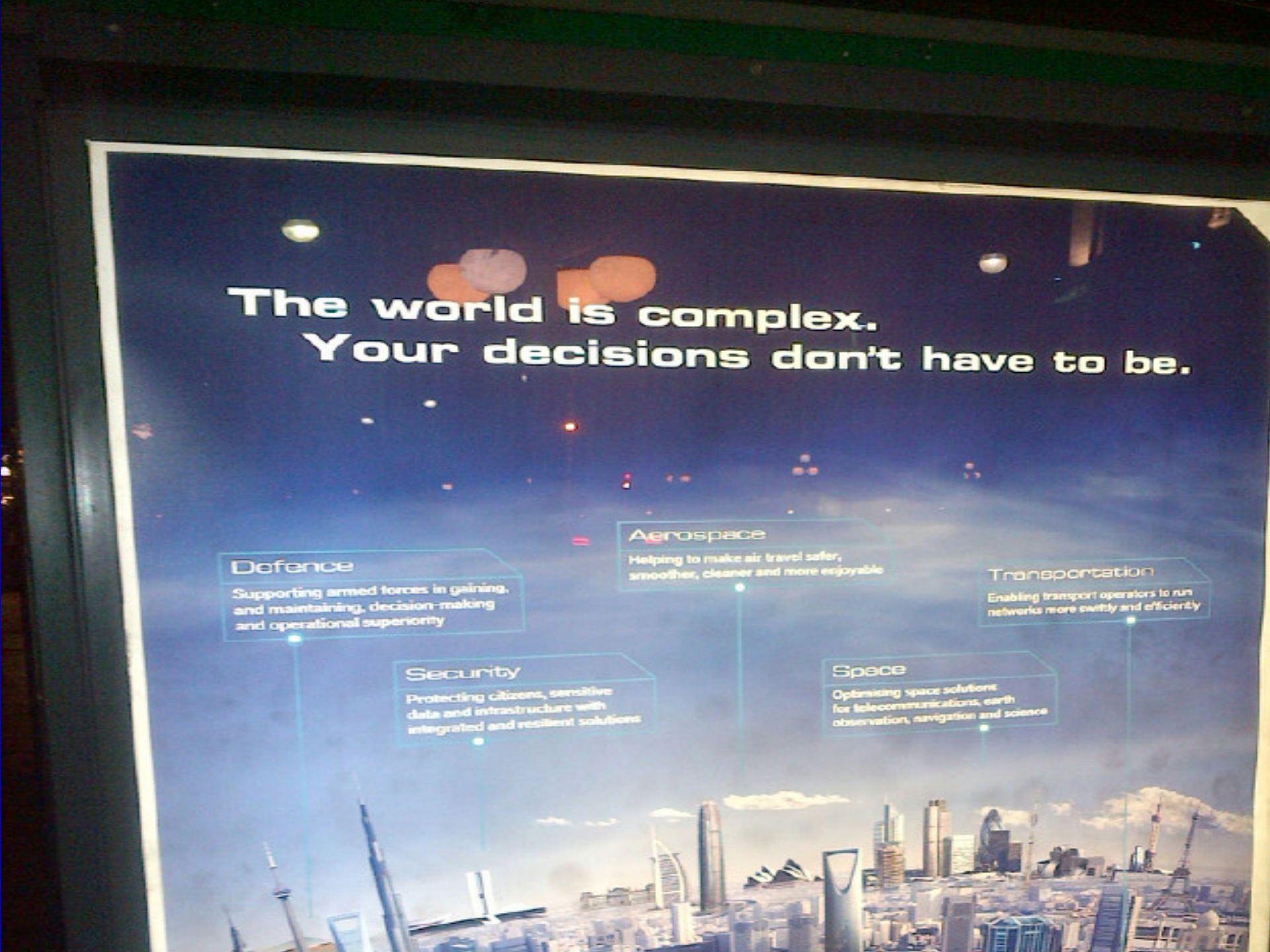
3. Epigenetics: relevance to complex disease:

Unlike DNA, epigenetic factors can be modified by developmental programs, hormones, environment, stochastic events, etc.

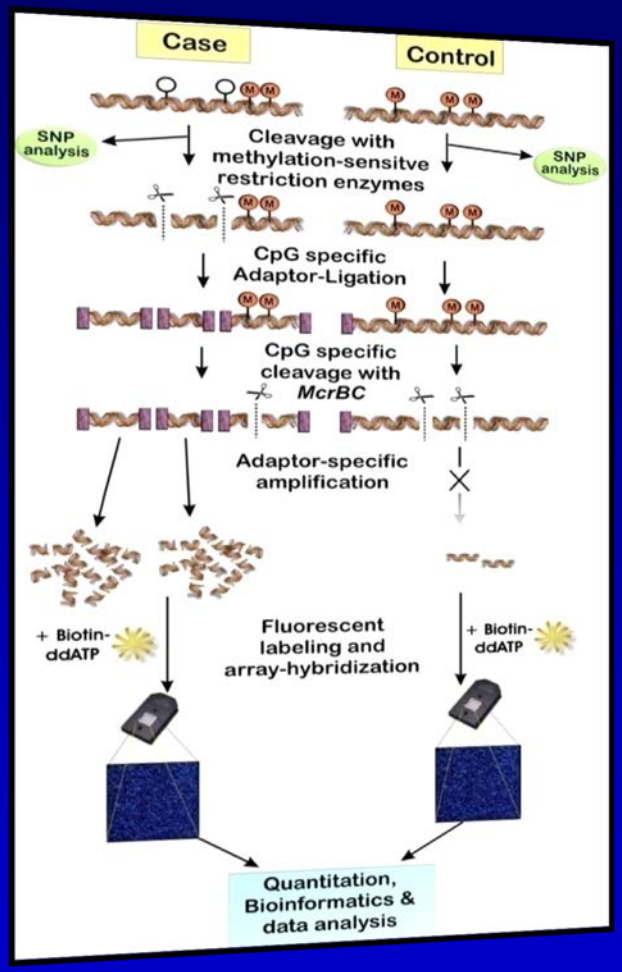


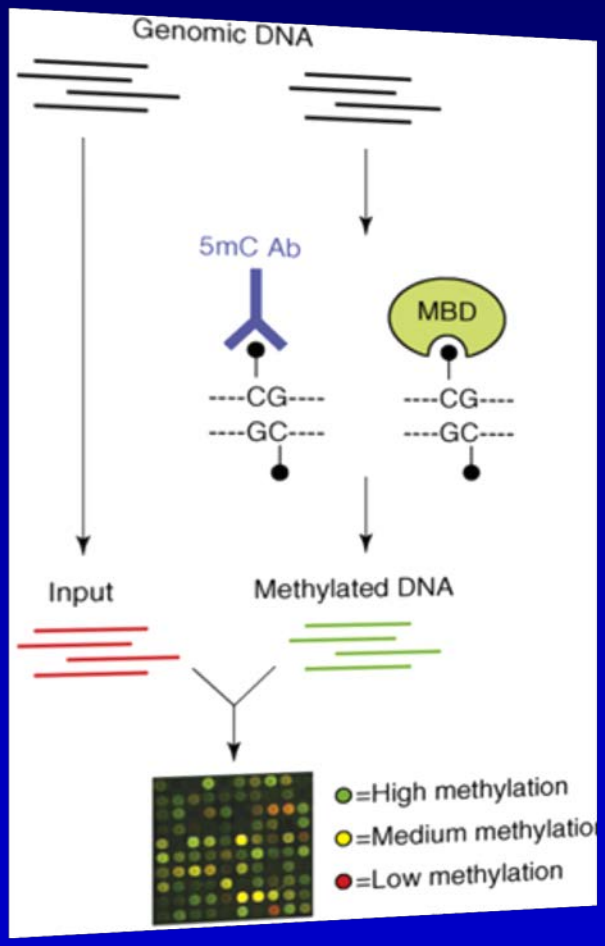


Petronis, *Nature* 2010


The world is complex.
Your decisions don't have to be.
Defence
Supporting armed forces in gaining, and maintaining, decision-making and operational superiority
Aerospace
Helping to make air travel safer, smoother, cleaner and more enjoyable
Transportation
Enabling transport operators to run networks more swiftly and efficiently
Security
Protecting citizens, sensitive data and infrastructure with integrated and resilient solutions
Space
Optimising space solutions for telecommunications, earth observation, navigation and science

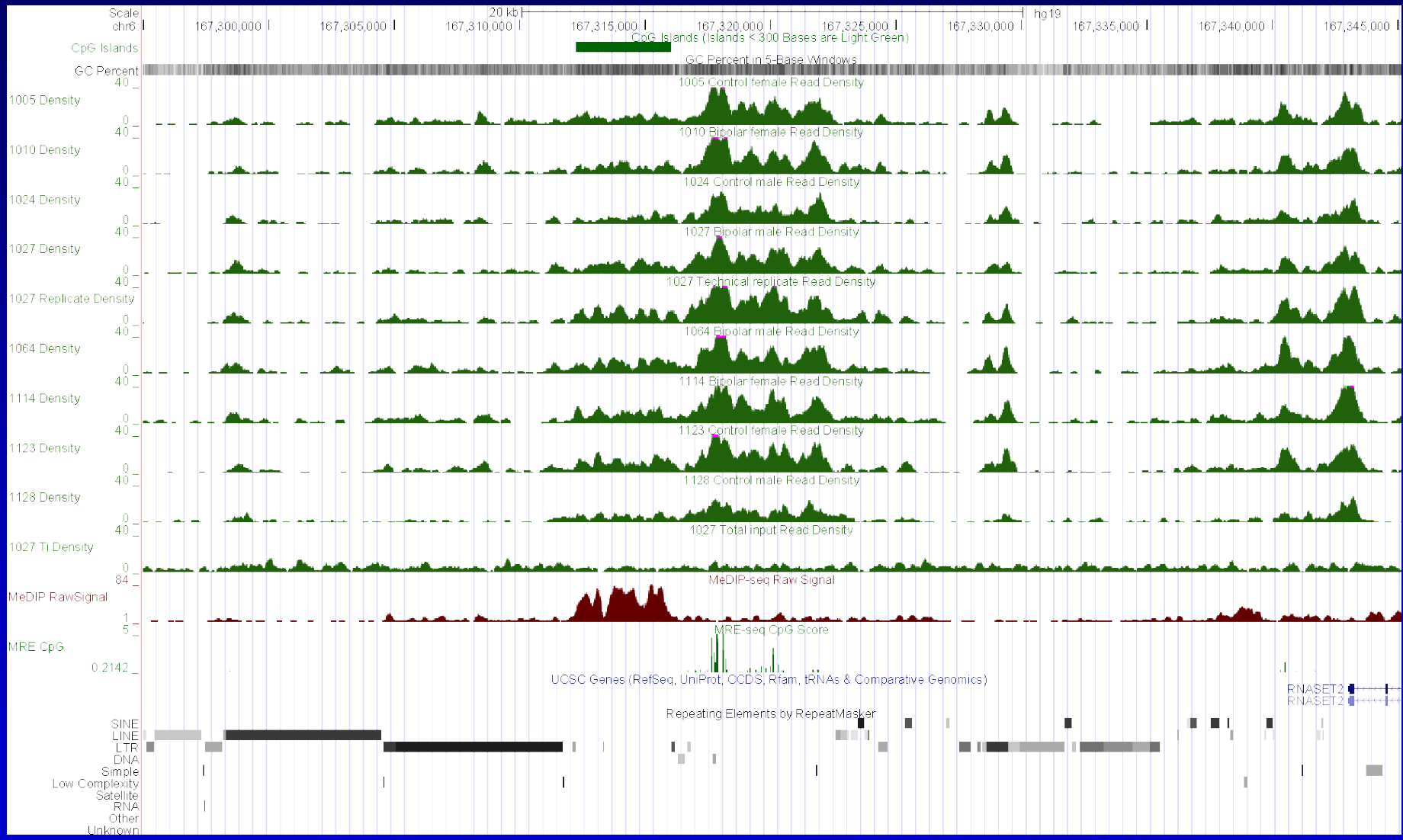
DNA modification profiling





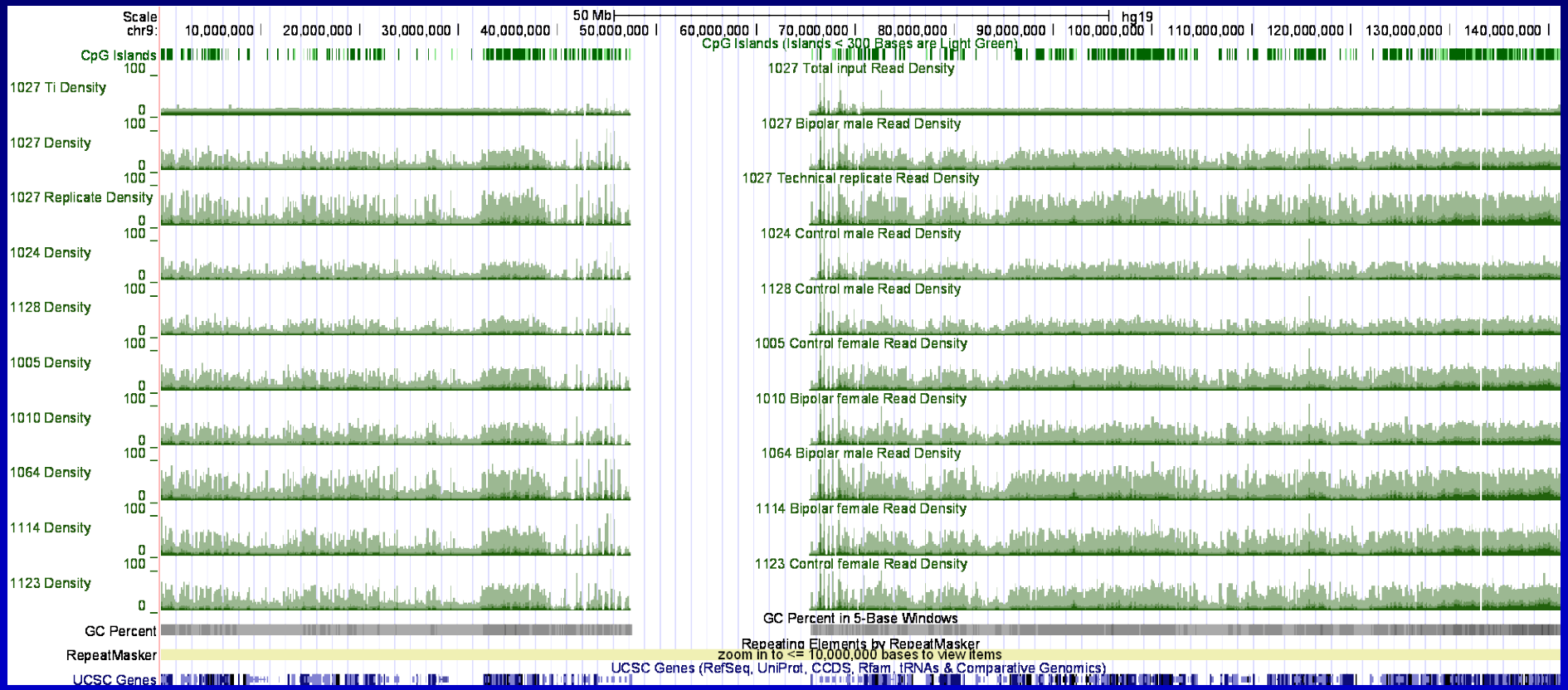
Enrichment of unmethylated or methylated fraction of genomic DNA

Human DNA modification profiles: 40 Kb



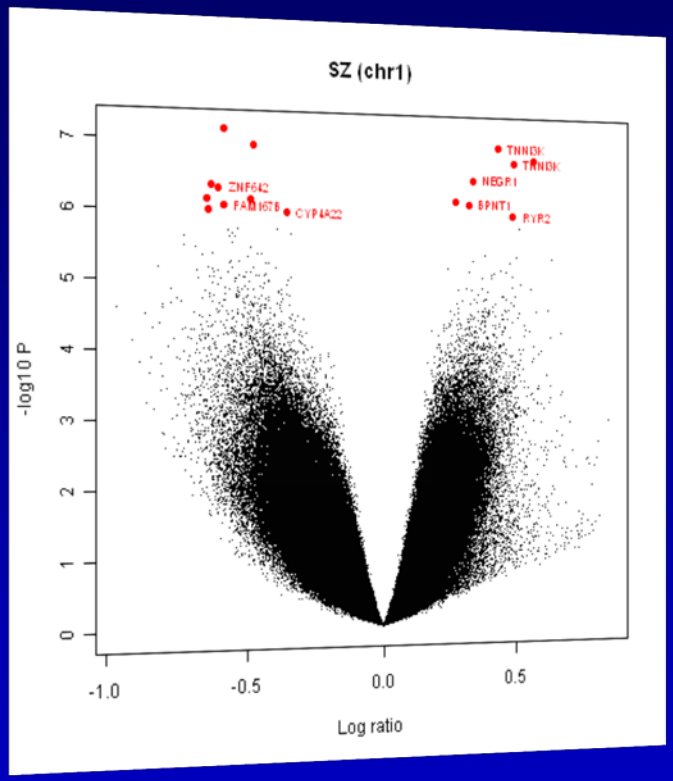
CAMH Krembil Epigenetics lab, *unpublished*

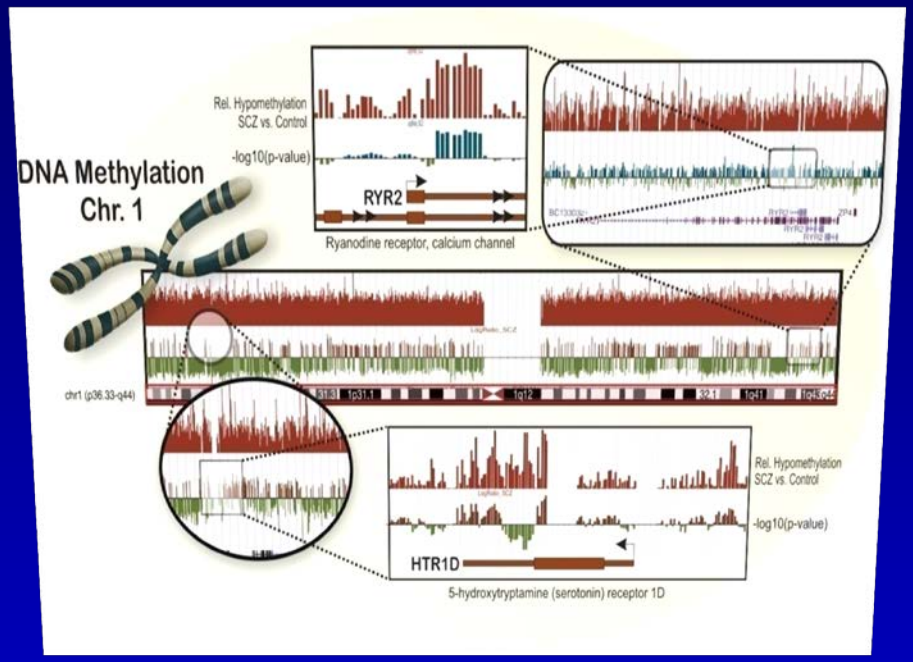
Human DNA modification profiles: 140 Mb (entire chromosome 9)



CAMH Krembil Epigenetics lab, *unpublished*

DNA methylome analysis in major psychosis: the first 15% of genome



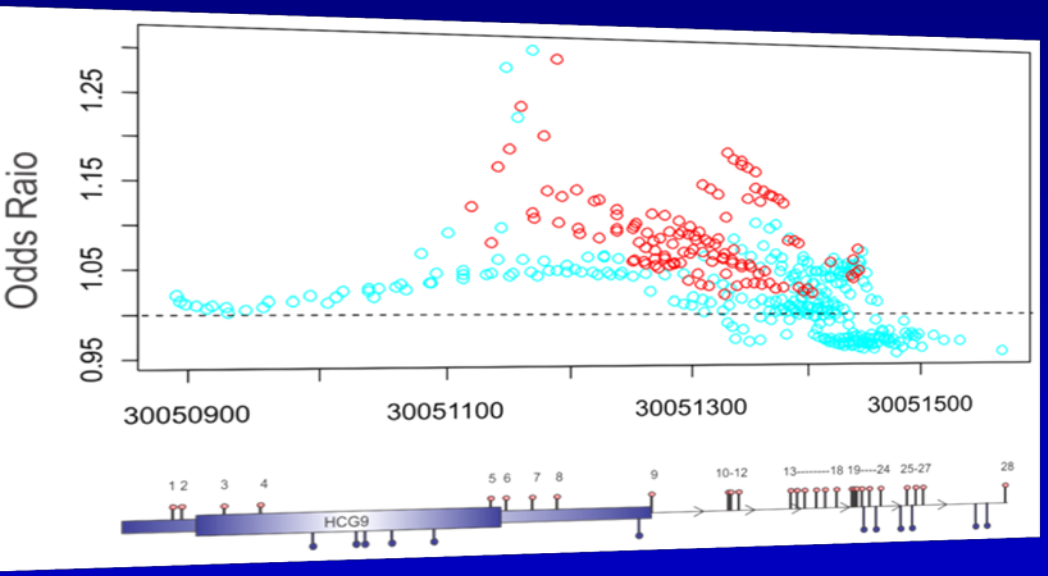


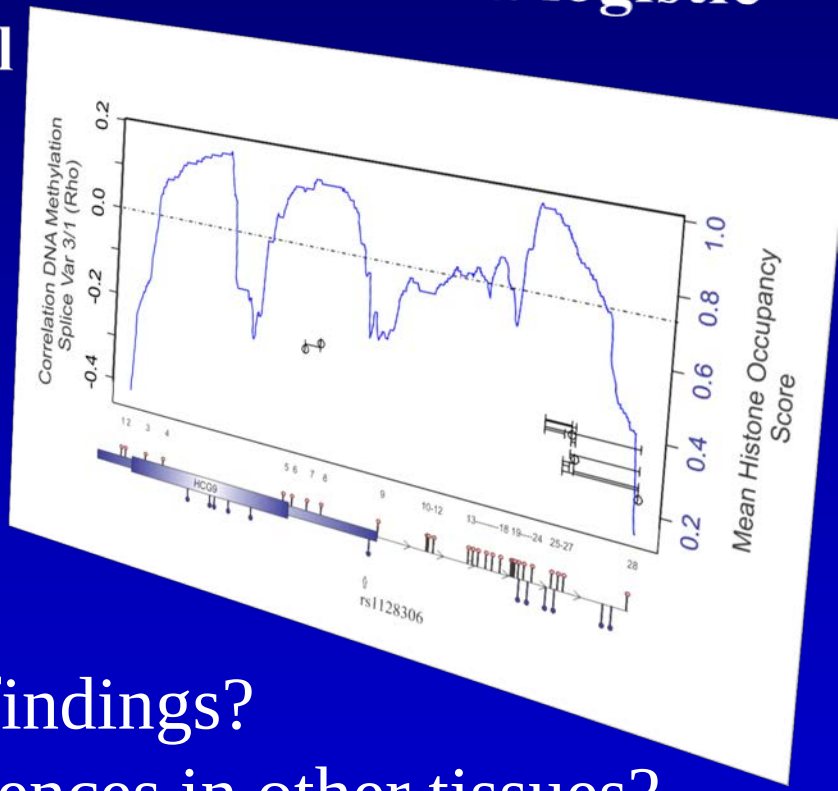
~100 post-mortem brains from major psychosis patients and controls
Enrichment of the unmethylated fraction of brain DNA
Interrogation on tiling microarrays (Affymetrix)

Key question: can we detect disease specific epigenetic differences?

Fine mapping of *HCG9* methylation differences in bipolar disorder: 1,400 samples from brain, peripheral blood, and sperm.

The rs1128306 SNP and age were modeled as covariates in a logistic regression model





Can we replicate the microarray findings?

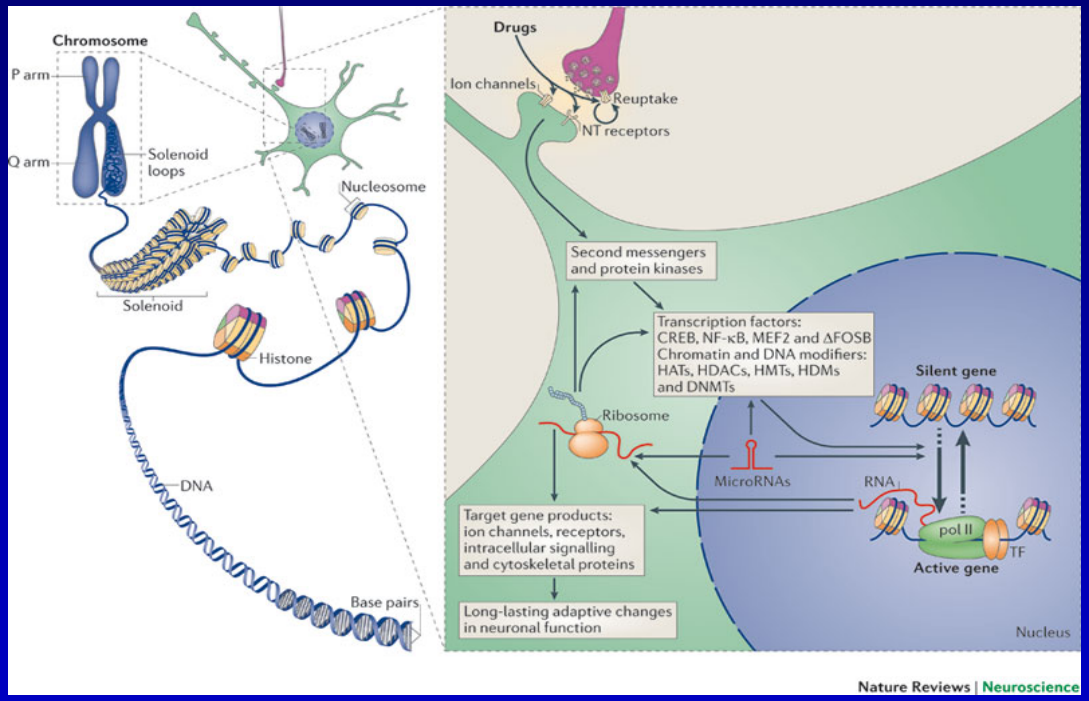
Can we detect similar epiG differences in other tissues?

Can we understand the mechanism of action?

Kaminsky et al. Mol Psychiatry 2012

How does a drug change the brain in fundamental and long-lasting ways?

- Some of the drug-induced changes at the chromatin level are extremely stable and thereby may underlie the long-lasting behaviours that define addiction.

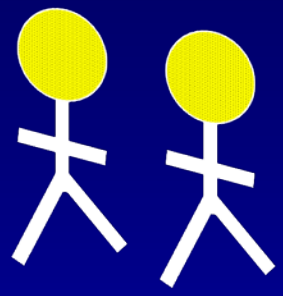


- Epigenetic studies revealed ~3,000 cocaine-induced H3K9me3 differential sites and more than 9,000 morphine-induced H3K9me2 differential sites in NAc, most of which are located at repetitive genomic sequences

Nestler et al. 2011, 2013

Origin of the paradigm: twin studies

Environment and Genes (DNA)

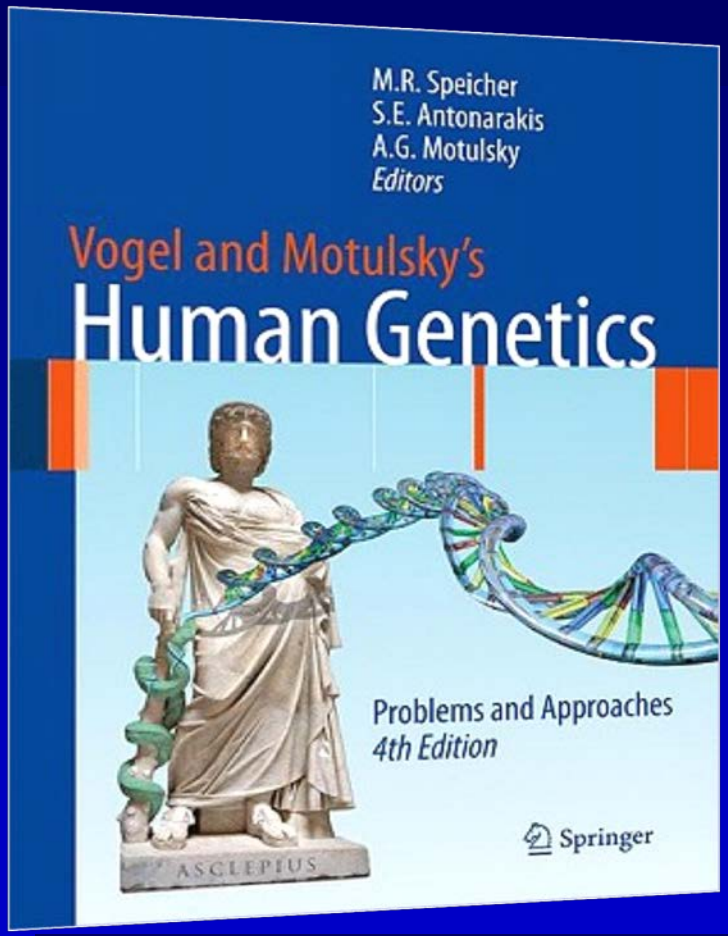


Monozygotic twins
(100% DNA identity)

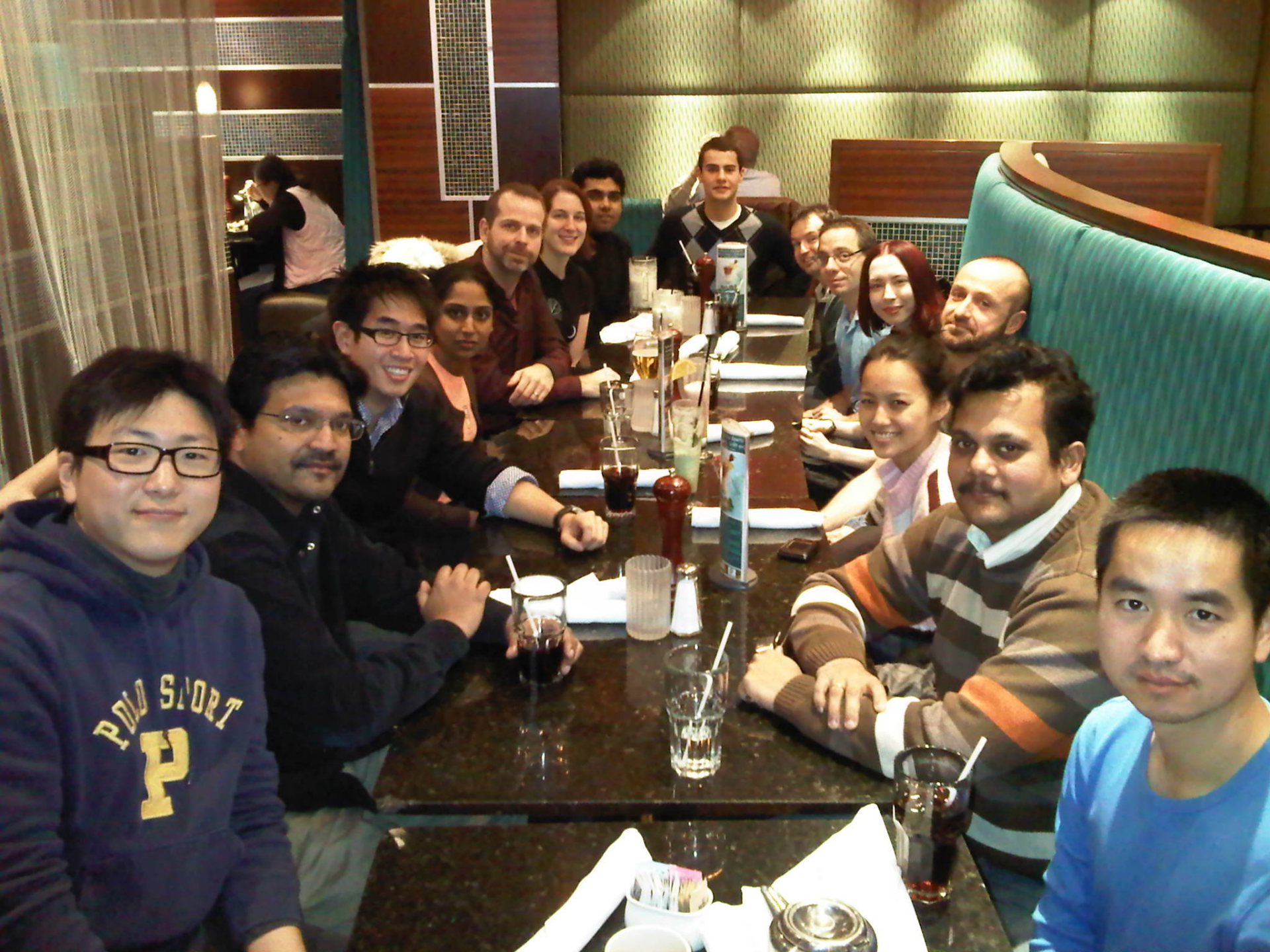
Dizygotic twins
(genetically different:
50% of segregating
polymorphisms;
Still 99.5% of DNA identity)

1. Discordance of MZ twins means environmental contribution
2. Discordance of DZ > MZ means heritability (=DNA variation)

Our goal is to trace genetic differences to the DNA level



F. Vogel and A.G. Motulsky., *Human Genetics: Problems and Approaches*. 1997; 807 p.


POLO SPORT