



Epigenetics, a possible biological mediator of environmental (and genetic) influences on (aggressive) behaviour

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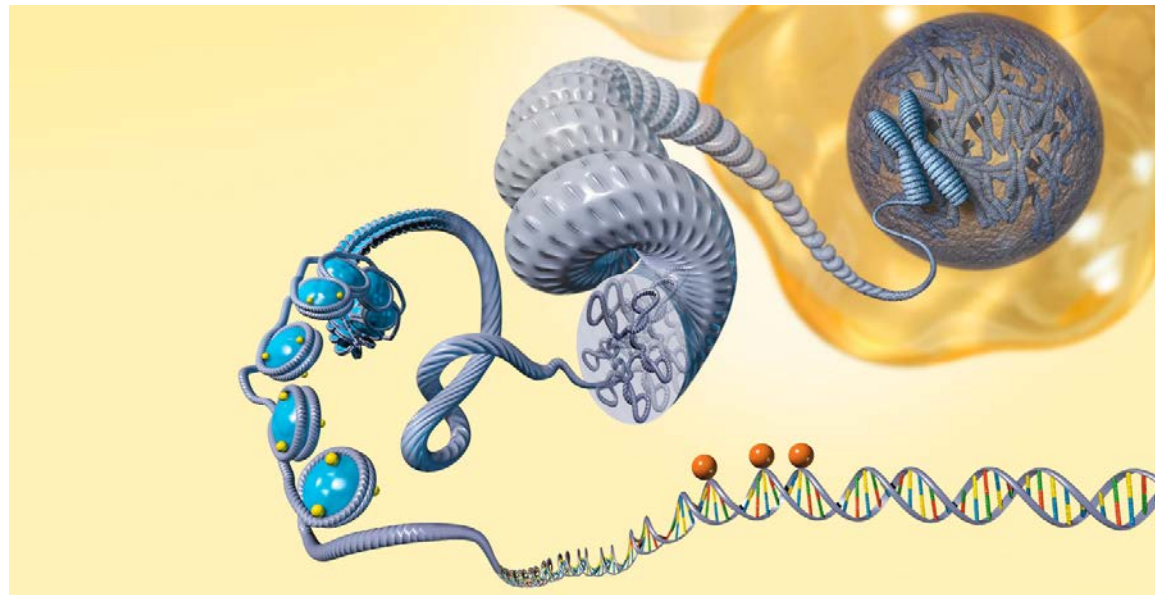


Epigenetics



- *epi-* (Greek: *επι-* over, above)
- epigenetics= “Above Genetics”

Epigenetics= The study of molecular mechanisms that influence the activity of gene expression and that are transmitted across cell division. [definition by Bird 2007 Nature]

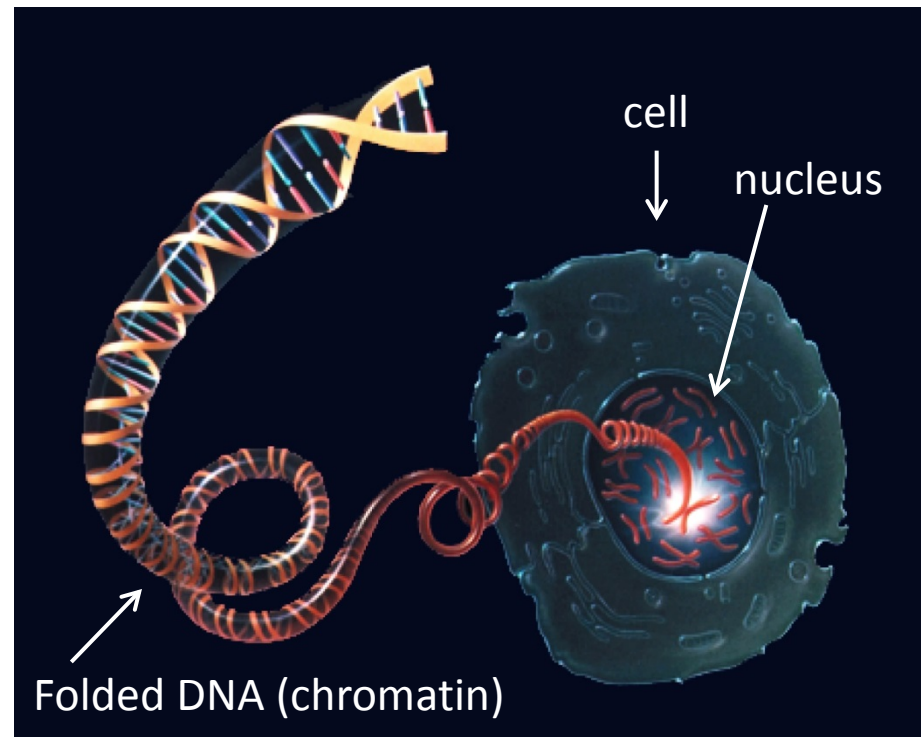




Function of epigenetic mechanisms

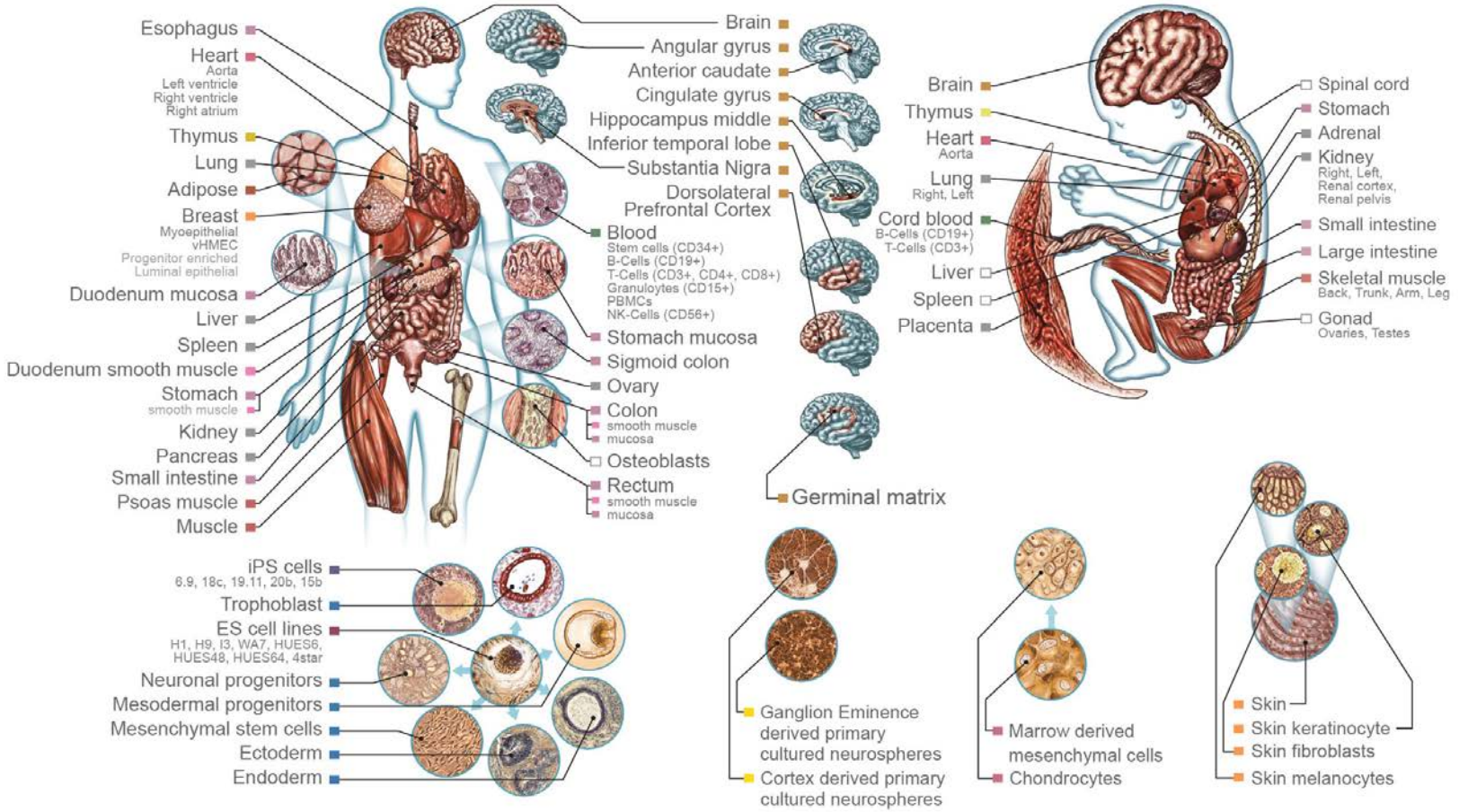


1. Fold the entire human genome (approximately 2 meters of DNA) into each cell nucleus (average diameter of 6 micrometers)
2. Regulate gene expression (e.g. tissue-specific expression, regulation of development)

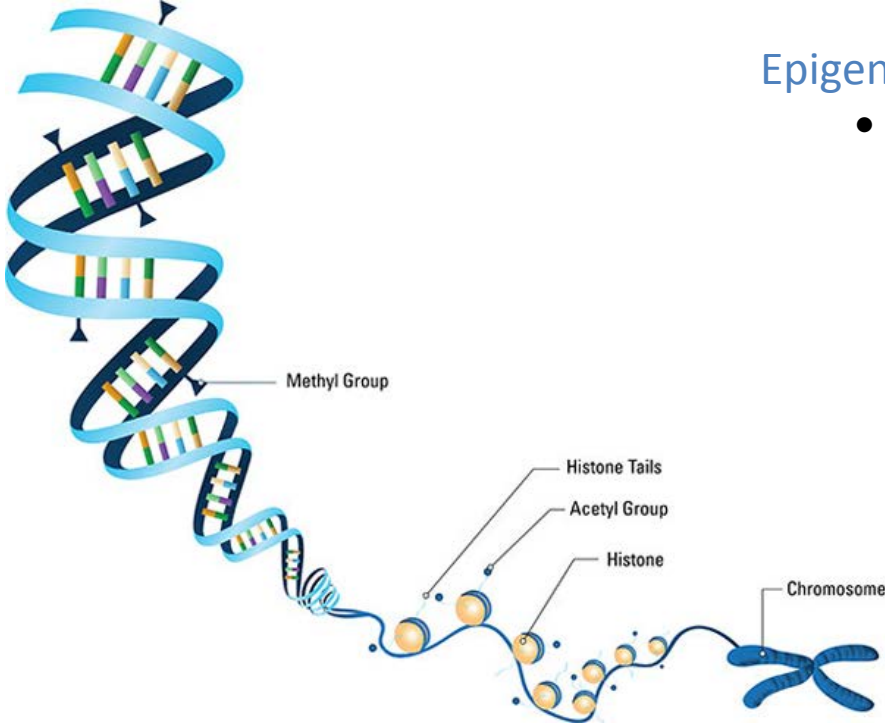




Each cell has its own *epigenome*

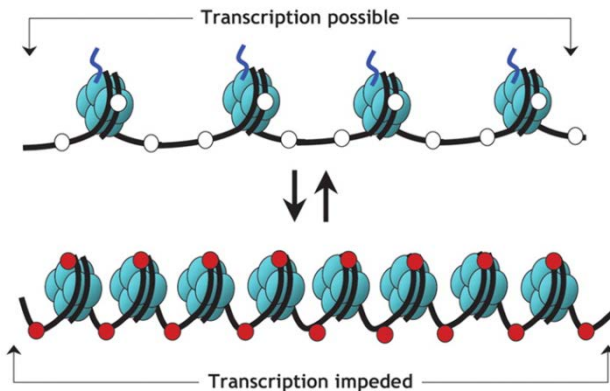


Kundaje, A, et al. "Integrative analysis of 111 reference human epigenomes." Nature 518.7539 (2015): 317-330.



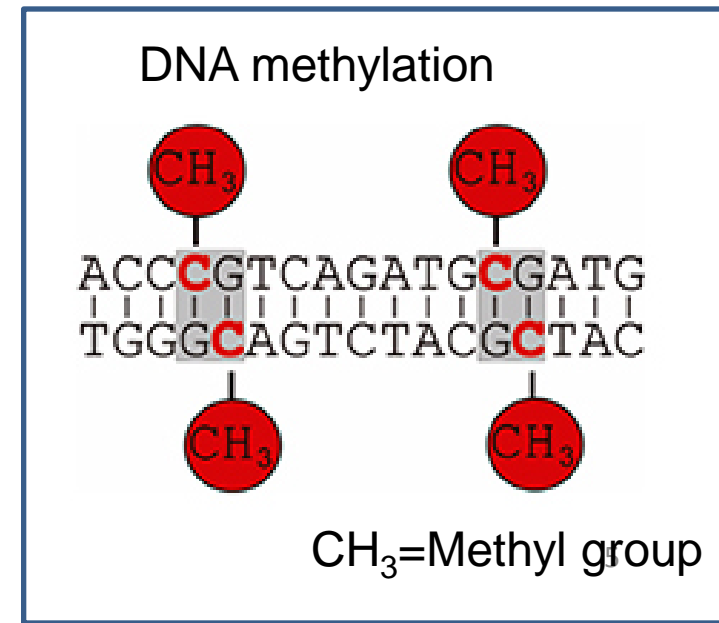
Epigenetic mechanisms

- DNA methylation (at cytosines next to guanines=**CpG sites**)
 - at promoters: usually represses gene expression
 - in gene bodies: may regulate alternative splicing
 - at enhancers - strongest relation to expression
- Histone modifications (e.g. histone methylation, histone acetylation)
- Many (potential) others: MicroRNAs, Prions, Interactions between DNA and DNA-binding proteins



Not all gene expression regulation is epigenetic!

Epigenetic = transmitted during cell division to daughter cells.





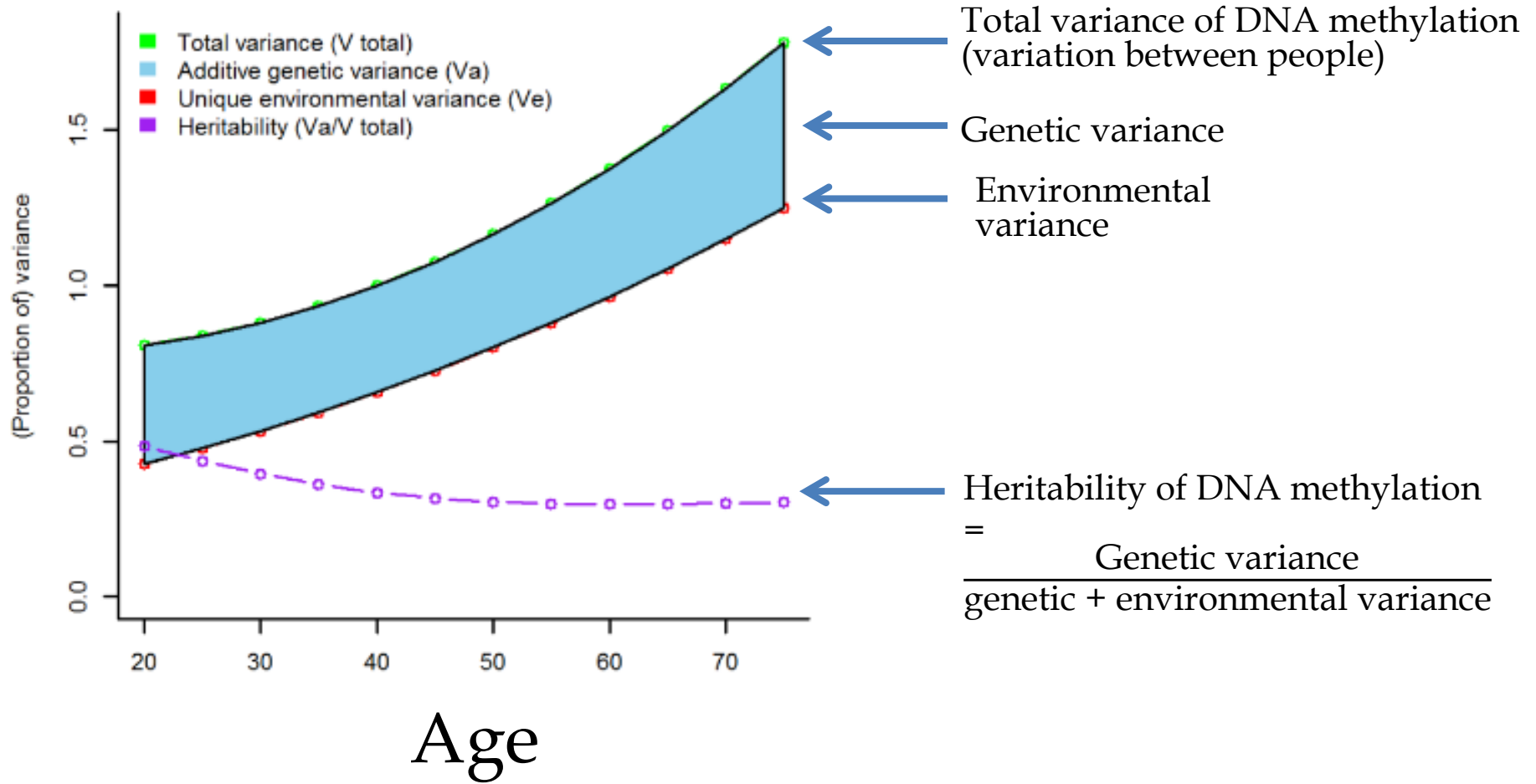
Variation in DNA methylation between people

- Variation in DNA methylation between people → variation in gene expression
- **Twin studies:** Average heritability of methylation levels in adults across 450.000 sites in the genome ~19%
(Illumina 450k array, peripheral blood, refs 1,2)
 - DNA-sequence contributes to its own regulation
 - Environment accounts for a large part of variation between people

Variation in DNA methylation – adult lifespan



~10% of genome-wide methylation sites in whole blood (Illumina 450k array)

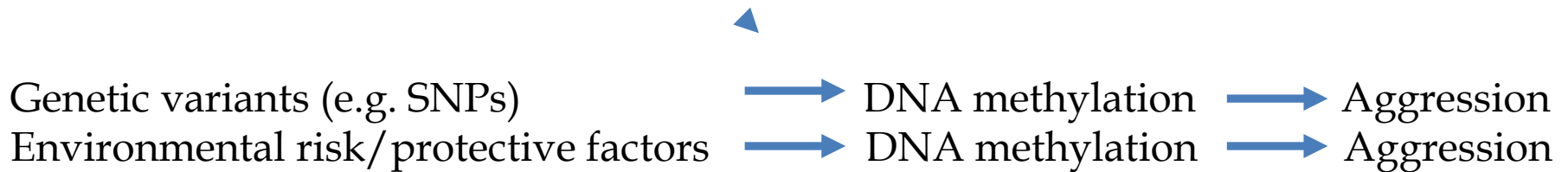




Potential role of epigenetics in Aggression



- **Known environmental influences** affecting DNA methylation:
(maternal) smoking and diet, (early) life conditions
- Genetic influences affecting DNA methylation: methylation QTLs
(e.g. single nucleotide polymorphisms)





Maternal smoking and DNA methylation



ARTICLE

DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis

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- Pregnancy And Childhood Epigenetics (PACE) consortium: 13 cohorts (n =6,685)
- **newborn blood DNA methylation** - maternal smoking during pregnancy
- **Over 6,000 CpGs** were differentially methylated in relation to maternal smoking
- Several genes are relevant to diseases that can be caused by maternal smoking (e.g., orofacial clefts and asthma) or adult smoking (e.g., certain cancers).
- Enrichment in pathways and processes critical to development.

Long-term effects of early environment



- Many diseases and (aggressive) behavior are linked to (early) life events/exposures
- How can a prenatal/childhood exposure affect behavior/disease decades later?

 Certain exposures may induce stable epigenetic changes

Epigenetic programming by maternal behavior (Weaver et al 2004):

- Persistent changes **DNA methylation** and expression of the glucocorticoid receptor gene in the **hippocampus**

→ Altered stress response in adulthood

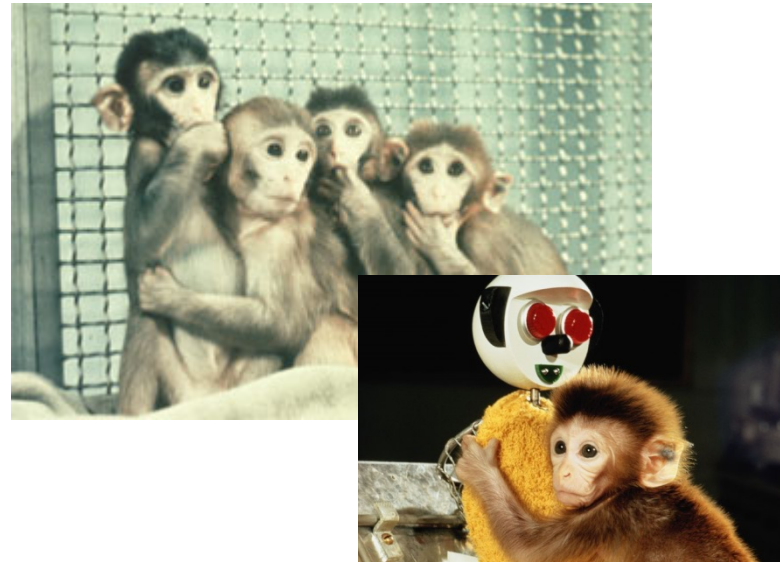




DNA methylation - Aggression



1. Maternal rearing condition



2. Surrogate mother+ peer-rearing condition
Inadequate social skills, highly aggressive, increased voluntary alcohol consumption

Nadine Provencal, Matthew J. Suderman, Claire Guillemin, Renaud Massart, Angela Ruggiero, Dongsha Wang, Allyson J. Bennett, Peter J. Pierre, David P. Friedman, Sylvana M. Côté, Michael Hallett, Richard E. Tremblay, Stephen J. Suomi and Moshe Szyf **The Signature of Maternal Rearing in the Methylome in Rhesus Macaque Prefrontal Cortex and T Cells.** *The Journal of Neuroscience* 32.44 (2012): 15626-15642.



DNA methylation – Aggression: Human studies



OPEN ACCESS Freely available online



Differential DNA Methylation Regions in Cytokine and Transcription Factor Genomic Loci Associate with Childhood Physical Aggression

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Association of Childhood Chronic Physical Aggression with a DNA Methylation Signature in Adult Human T Cells

Nadine Provençal^{1,2,3*}, Matthew J. Suderman^{1,3,6*}, Claire Guillemain^{1,2,3}, Frank Vitaro^{2,7}, Sylvana M. Côté^{2,8}, Michael Hallett⁶, Richard E. Tremblay^{2,4,5*}, Moshe Szyf^{1,3*}

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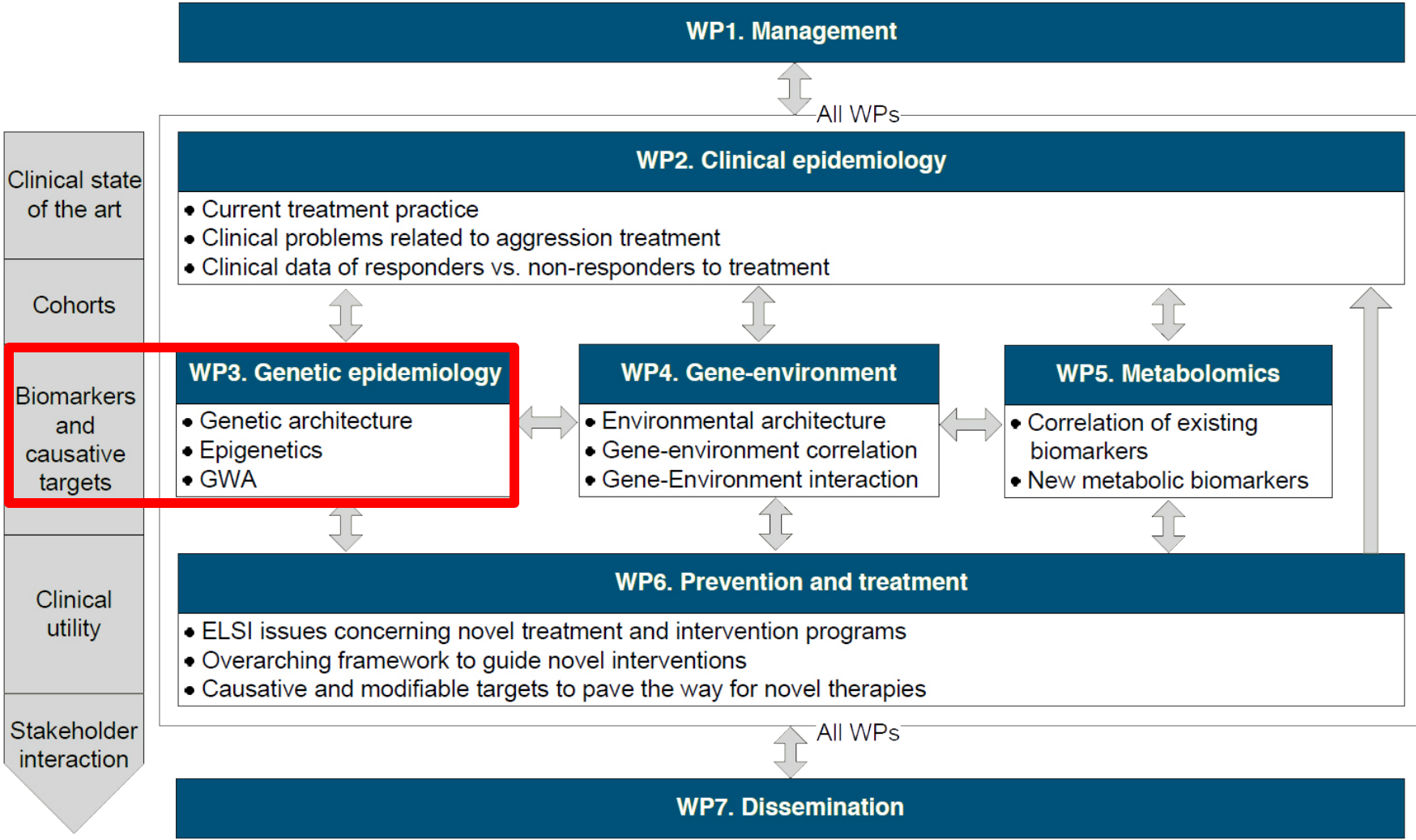
DNA Methylation Signature of Childhood Chronic Physical Aggression in T Cells of Both Men and Women

Claire Guillemain^{1,2,3}, Nadine Provençal^{1,2,3}, Matthew Suderman^{1,3,7}, Sylvana M. Côté^{2,6,9}, Frank Vitaro^{2,8}, Michael Hallett⁷, Richard E. Tremblay^{2,4,5,6*}, Moshe Szyf^{1,3*}

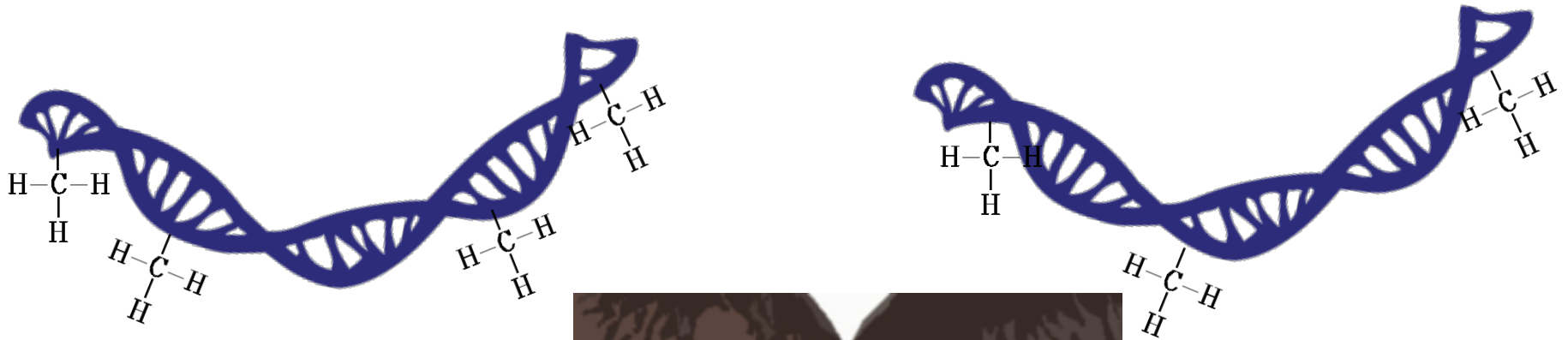
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ACTION aims to identify epigenetic mechanisms linked to aggression



ACTION: Identify epigenetic mechanisms linked to aggressive behavior



DNA methylation



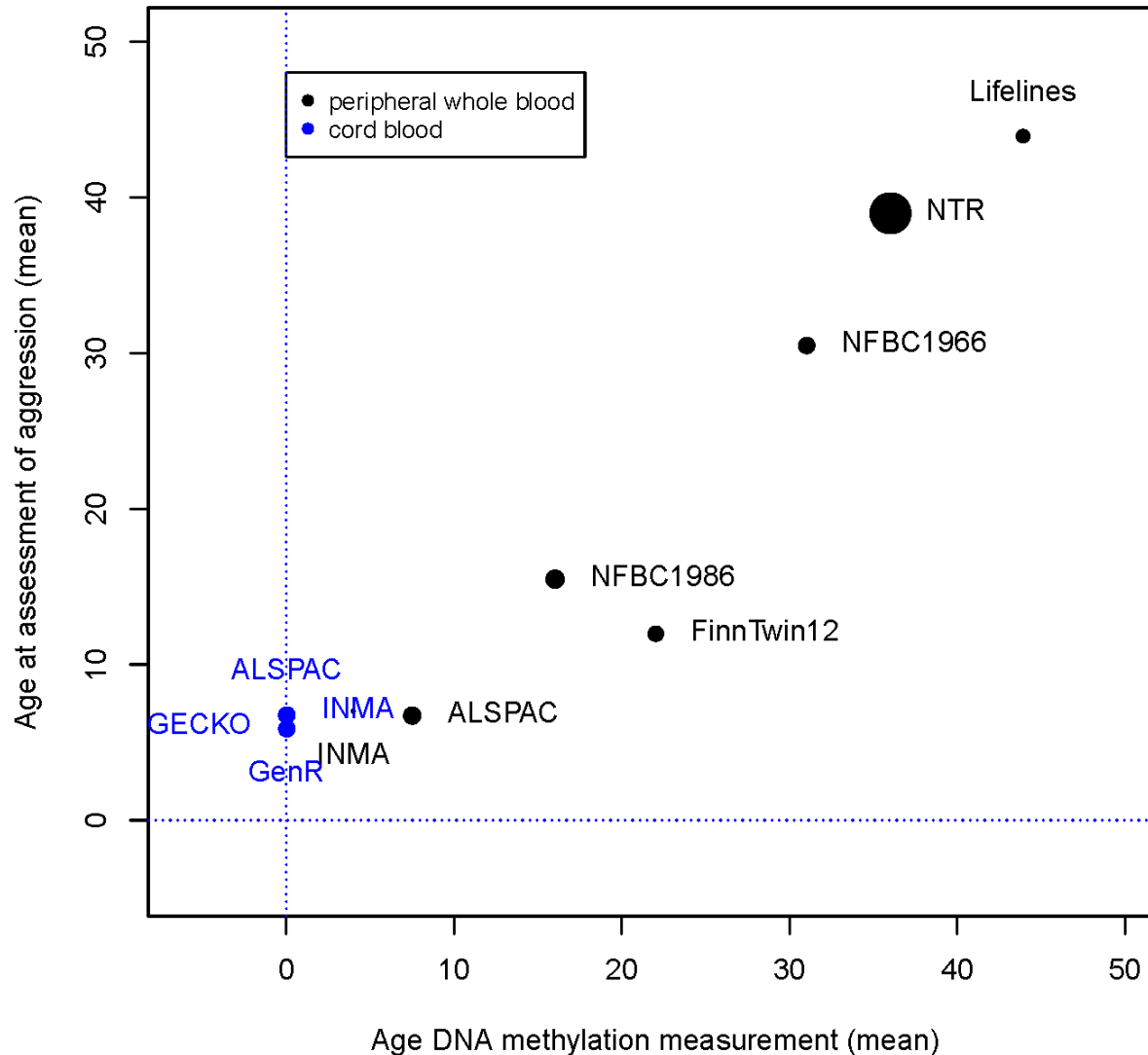
- Biological sample collection in monozygotic twins (buccal and urine)
- Measure DNA methylation in aggression *concordant* and *discordant* twins
- Measure biomarkers and metabolites



Epigenome-wide association study (EWAS) meta-analysis of aggressive behavior (Illumina 450k array)

Study abbreviation	Study	DNA source	Aggression data	N (PWB/UCB)
NTR	Netherlands Twin Register	PWB	ASEBA Adult self-report (ASR) aggression scale	2029
FT12	FinnTwin 12	PWB	Multidimensional Peer Nomination Inventory (MNPI) – aggressive behavior	757
GenR	Generation R	UCB	Child Behavior Checklist (CBCL) 1½ – 5 years Aggressive Behavior scale	806
LLD	LifeLines-DEEP	PWB	“I am known for being short-tempered and irritable” (NEO personality)	683
ALSPAC	Avon Longitudinal Study of Parents and Children	PWB /UCB	SQD conduct problem scale age 7	865/808
NFBC1966	Northern Finnish Birth Cohort 1966	PWB	“I lose my temper more quickly than most people” (TCI-NS4 Temperament and Character Inventory- Novelty Seeking)	803
NFBC1986	Northern Finnish Birth Cohort 1986	PWB	ASEBA Youth self-report (YSR) aggression scale	593
Gecko	Groningen Expert Center for Kids with Obesity	UCB	SDQ conduct problem scale age 6	198
INMA	Infancia y Medio Ambiente	PWB/UCB	SDQ conduct problem scale age 7	~200/~380
				N total ~6249

DNA methylation (Illumina 450k array) – aggressive behavior meta-analysis





DNA methylation peripheral tissues vs brain



RESEARCH PAPER

Epigenetics 10:11, 1024–1032; November 2015; Published with license by Taylor & Francis Group, LLC

Interindividual methylomic variation across blood, cortex, and cerebellum: implications for epigenetic studies of neurological and neuropsychiatric phenotypes

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RAPID PUBLICATION

DNA Extracted From Saliva for Methylation Studies of Psychiatric Traits: Evidence for Tissue Specificity and Relatedness to Brain

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medical genetics
Neuropsychiatric Genetics

PART
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- Variation at a subset of probes - strongly correlated across tissues.
- Hannon et al: At most DNA methylation sites: interindividual variation in whole blood is not a strong predictor of interindividual variation in the brain
- Smith et al: Compared to blood DNA methylation, saliva (buccal cells) DNA methylation levels=more similar to brain DNA methylation
- Hannon et al: “These results do not, however, discount the utility of using a blood-based EWAS to identify biomarkers of disease phenotypes manifest in the brain”.



Thank you for your attention

