



# Epigenetic Variation in Human Health and Disease

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**Centre for Molecular Medicine and Therapeutics**

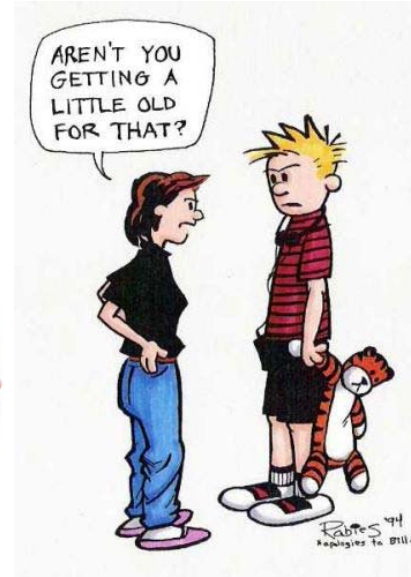
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**University of British Columbia**

[www.cmmmt.ubc.ca](http://www.cmmmt.ubc.ca)

# Understanding Epigenetics – a Journey Through Life

Epigenetics refers to persistent and heritable alterations in genome information that do NOT involve changes in DNA sequence



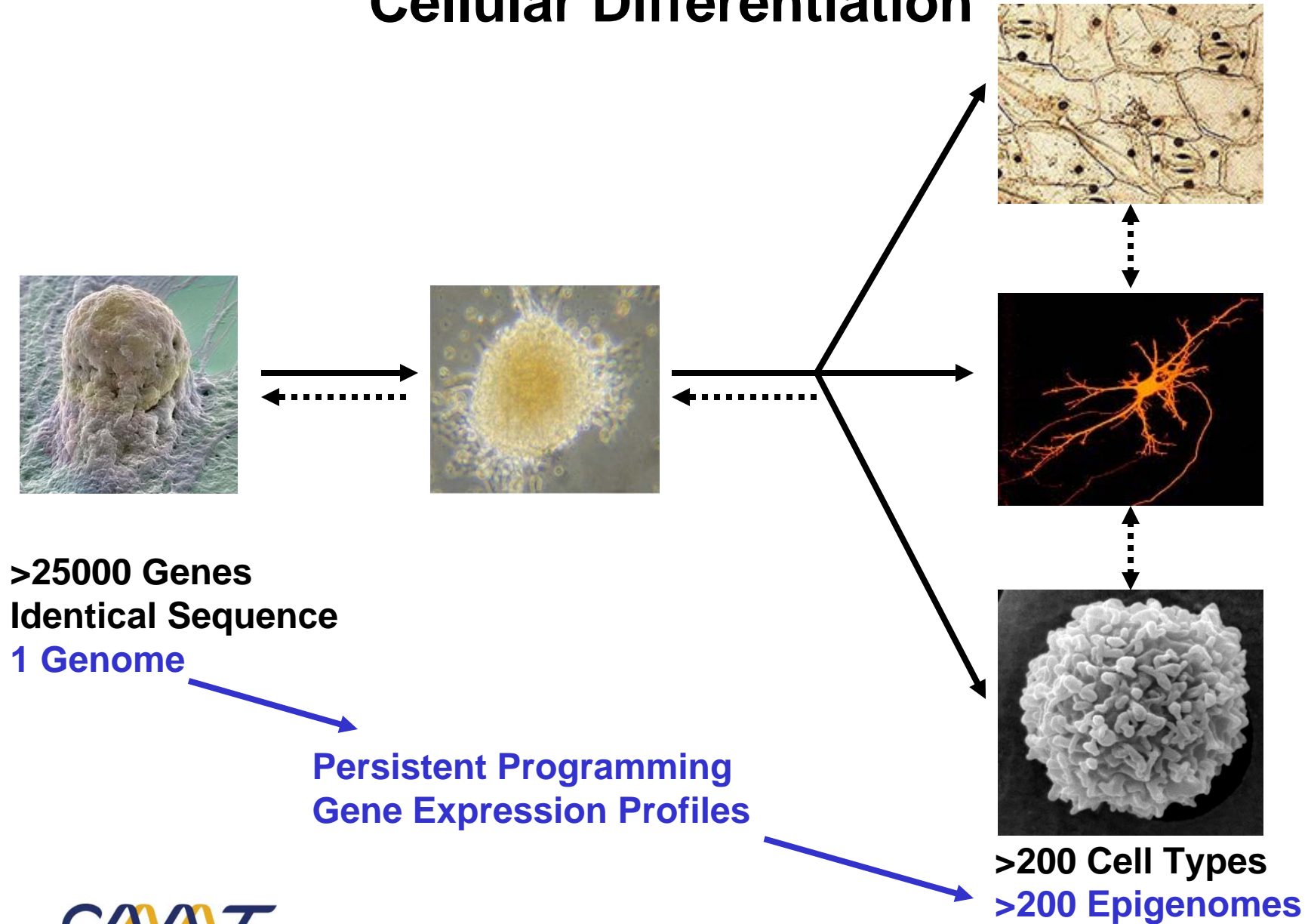
***Same Genome – Many Epigenomes***



**Developmental Epigenome Programming**  
**Environmental Influences on Epigenome**



# From Genome to Epigenomes – Cellular Differentiation



# Presentation Outline

Epigenetics at the Interface of Genome and Environment

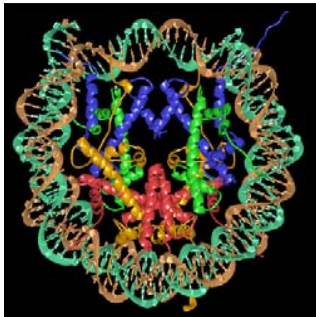
Epigenetic Variation in Adults

Biological Embedding of Early Life Experiences

Gene Expression and Pro-Inflammatory Phenotype

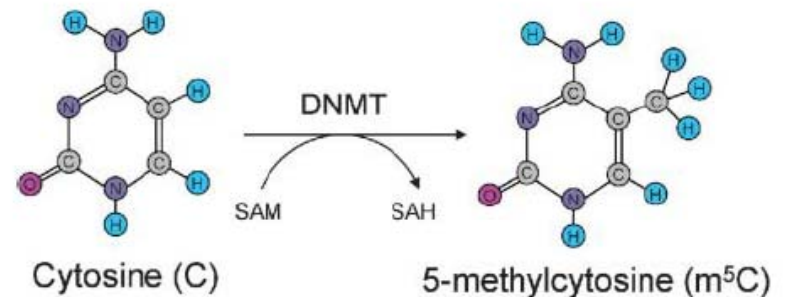
Epigenetic Vestiges of Family Environment

Genetic Determinants of Epigenetic Variation



Histone Modification  
Chromatin Remodeling  
Histone Variants  
RNA-Based Mechanisms

DNA Methylation



*“Epigenetic” Regulation of Gene Expression*



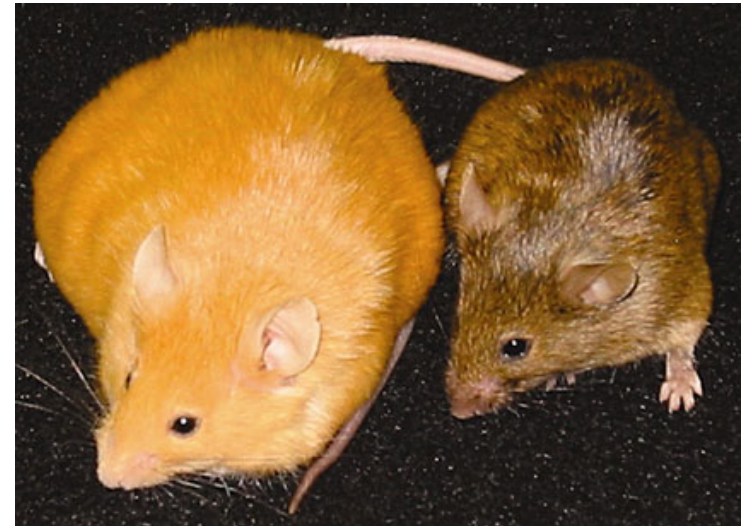
# Maternal Diet Affects Epigenetic Gene Regulation in Isogenic Offspring ( $A^{vy}/a$ )

Young Mice



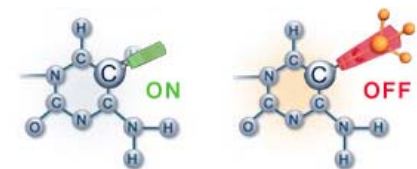
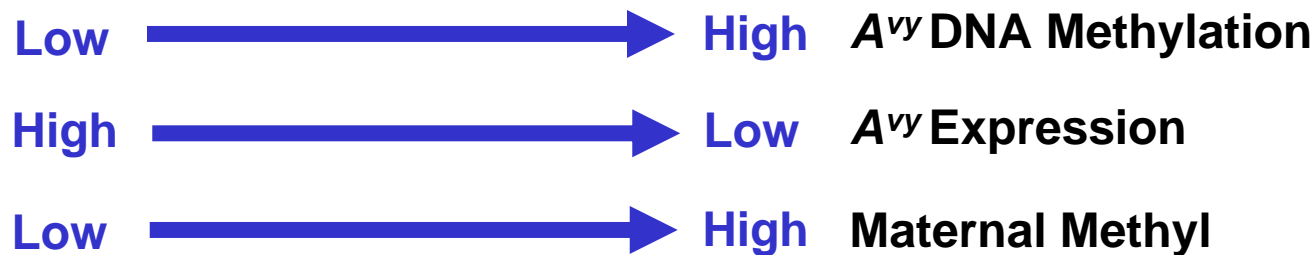
Yellow      Slightly mottled      Mottled      Heavily mottled      Pseudo-agouti

Adult Mice



Obese

Lean

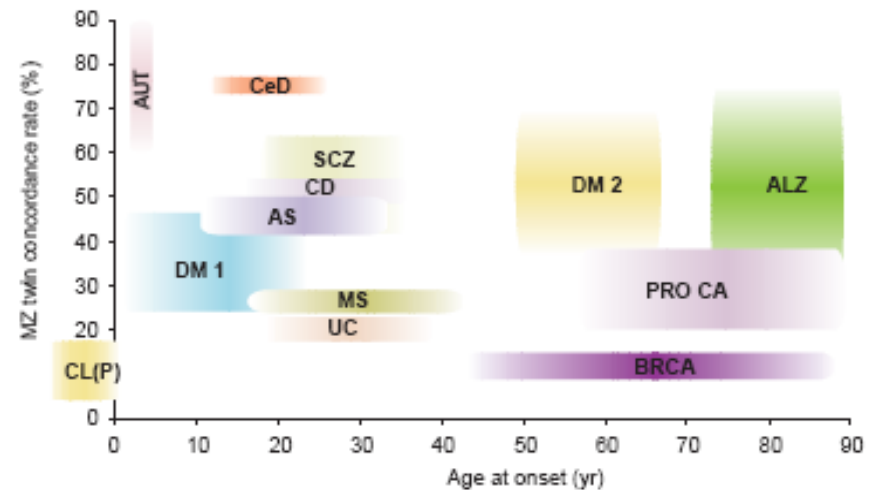


# Impact of Epigenetics on Health and Disease

Nutrition and lifestyle of mother affects epigenome of child



Identical twins acquire discordant epigenomes during life-course

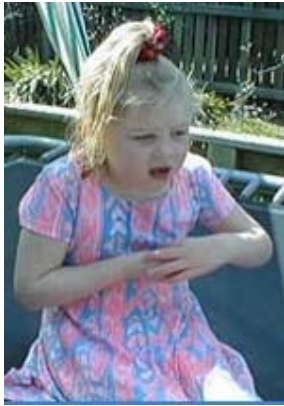


Maternal care affects epigenome of offspring



# Epigenetics in Population Health

Rett Syndrome  
**MECP2**

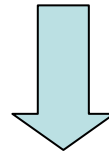


Rubinstein-Taybi Syndrome **CBP**



**Genes <-> Environment <-> Epigenetics**

**INTEGRATED**



**Disease Characteristics**

**Occurrence**

**Age of Onset**

**Severity**

**Prognosis**

**Biomarker Correlating with Disease**

**Epigenetic Therapies**



# Exploring Normative Human Epigenetic Variation

## Population Variation Discovery Cohort (N=33)

*DNA Methylation (1506 CpG sites)*

Peripheral Blood  
Mononuclear Cells (PBMC)

*Tissue Specificity*

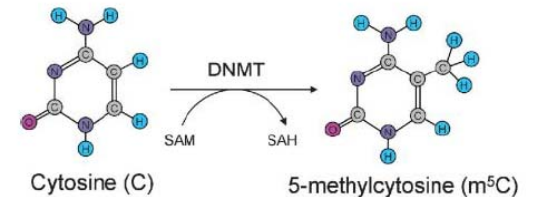
Buccal Swap Epithelial Cells

## Aging Cohort (N=60)

*DNA Methylation (28,000 CpG sites)*

Peripheral Blood  
Mononuclear Cells (PBMC)

*Developmental Trajectory*



## Genomic Embedding of Experiences Cohort (N=101)

*DNA Methylation (28,000 CpG sites)*

*Global mRNA Expression*

Peripheral Blood  
Mononuclear Cells (PBMC)

*Gene Expression Circuitry*



Edith Chen (University of British Columbia)  
Greg Miller (University of British Columbia)

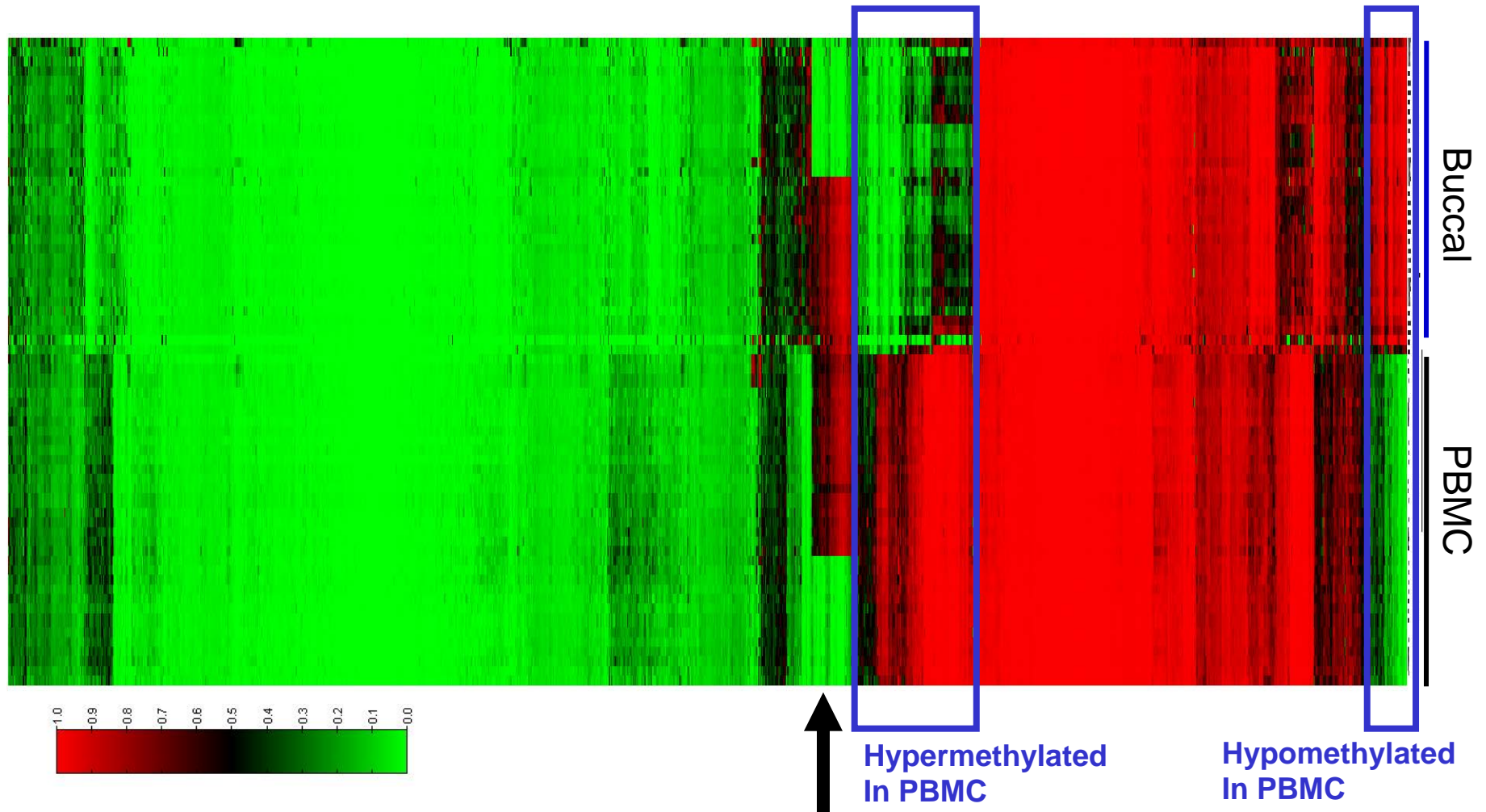
Mark Loeb (McMaster University)



# Landscape of Epigenetic Tissue Specificity

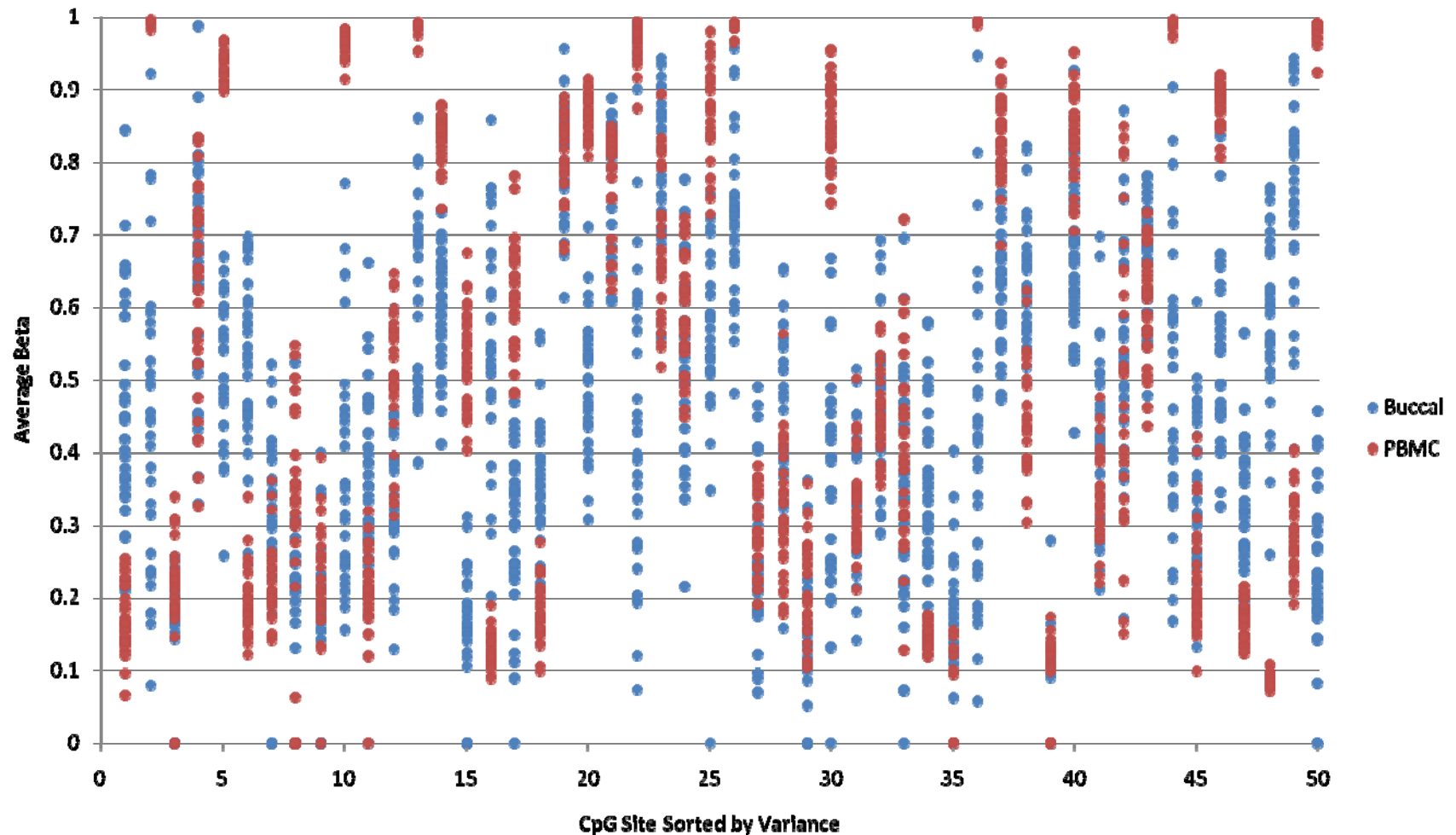
Buccal Swab vs PBMC - same individual:  $r^2 = 0.69$

PBMC/Buccal - 2 individuals same gender:  $r^2 = 0.94-0.96$



# Extensive Epigenetic Variation in Buccal Cells

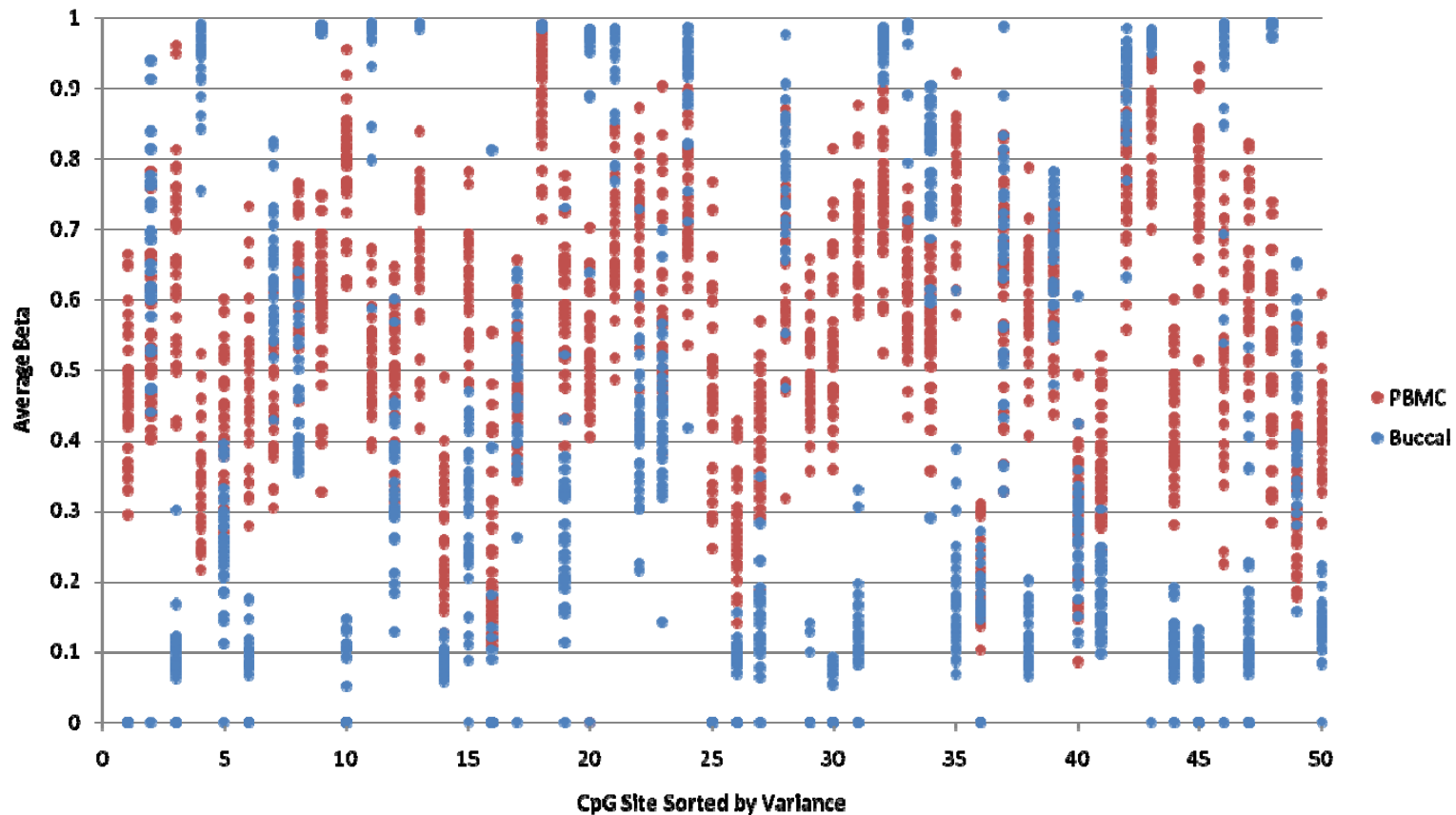
Top 50 Variable Sites in Buccal Compared to PBMC



*Epigenetic variation can be tissue specific*

# Extensive Epigenetic Variation in Peripheral Blood Mononuclear Cells

Top 50 Variable Sites in PBMC Compared to Buccal

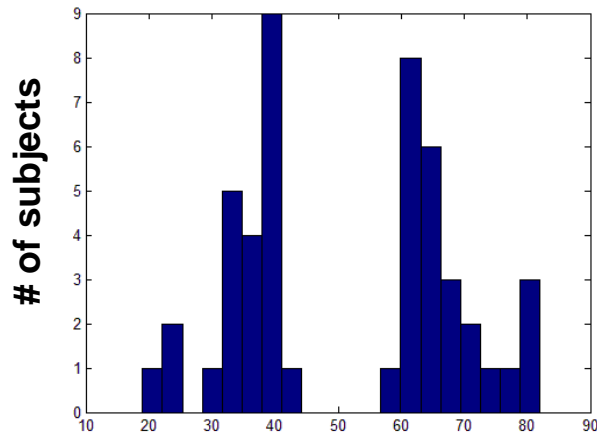


*Variation reproduced in 2<sup>nd</sup> larger genomic embedding cohort*

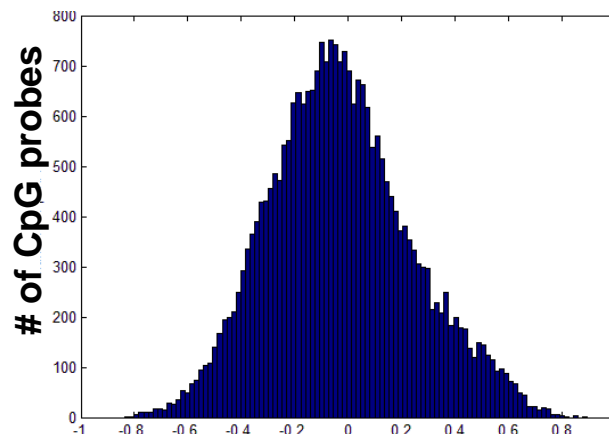
*Relatively low correlation of promoter DNA methylation and gene expression*



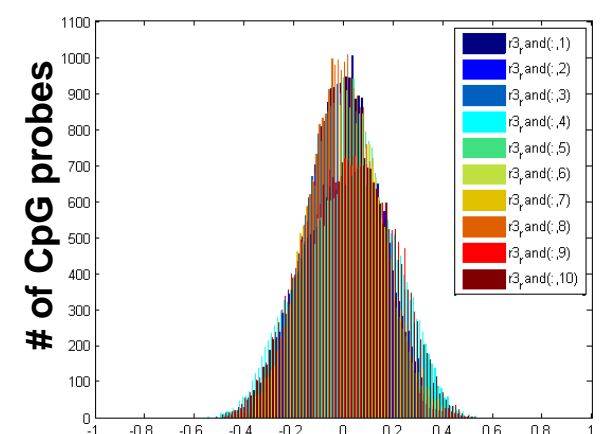
# DNA Methylation Correlated with Aging



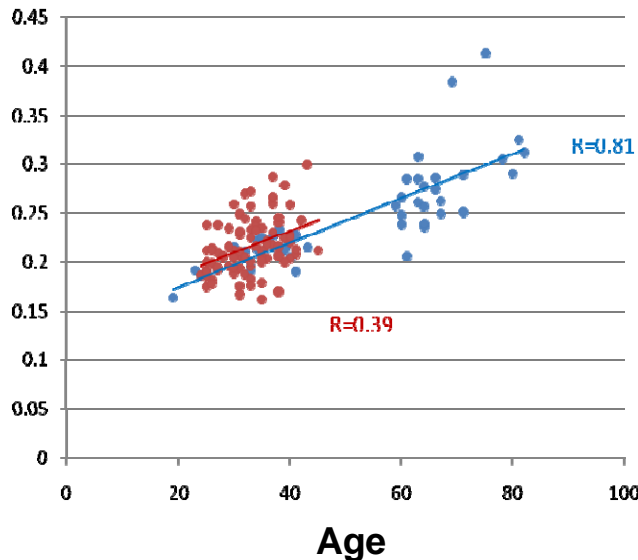
Age distribution of subjects assayed for DNA methylation



Spearman correlation of DNA methylation and age



Spearman correlation of randomized dataset



●  $\text{cg00503840 ML}$   
●  $\text{cg00503840 CL}$   
— Linear ( $\text{cg00503840 ML}$ )  
— Linear ( $\text{cg00503840 CL}$ )

Representative age-correlated  
CpG locus reproduced in **2<sup>nd</sup>**  
**cohort with narrow age-range**

Canadian Longitudinal Study on Aging (CLSA)  
Parminder Raina, McMaster University

Genetics and Epigenetics Centre of CLSA  
Michael Hayden, Max Cynader, Michael S. Kobor



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Biological Embedding of Early Life Experiences

Gene Expression and Pro-Inflammatory Phenotype

Epigenetic Vestiges of Family Environment



*Early Life Socio-Economic Status*



*Early Life Parental Stress Level*

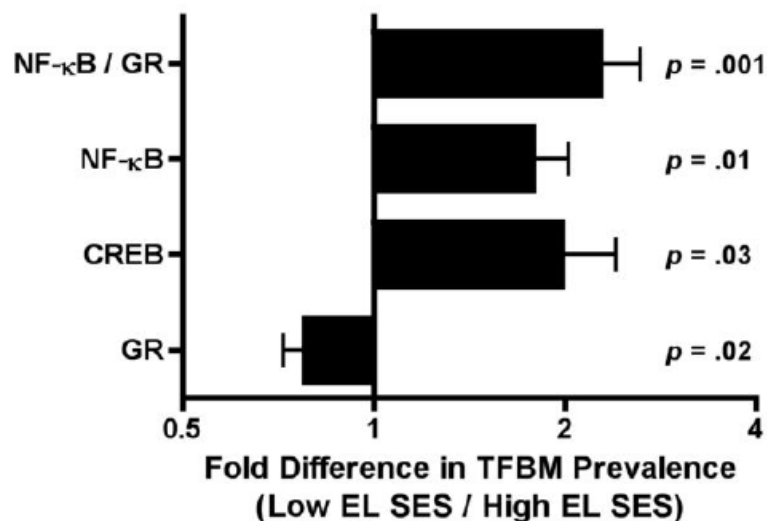




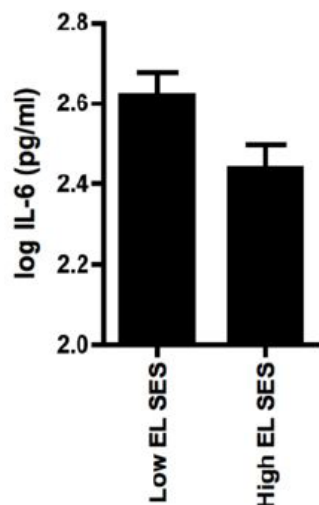
# Biological Residue of Low Early-Life Social Class



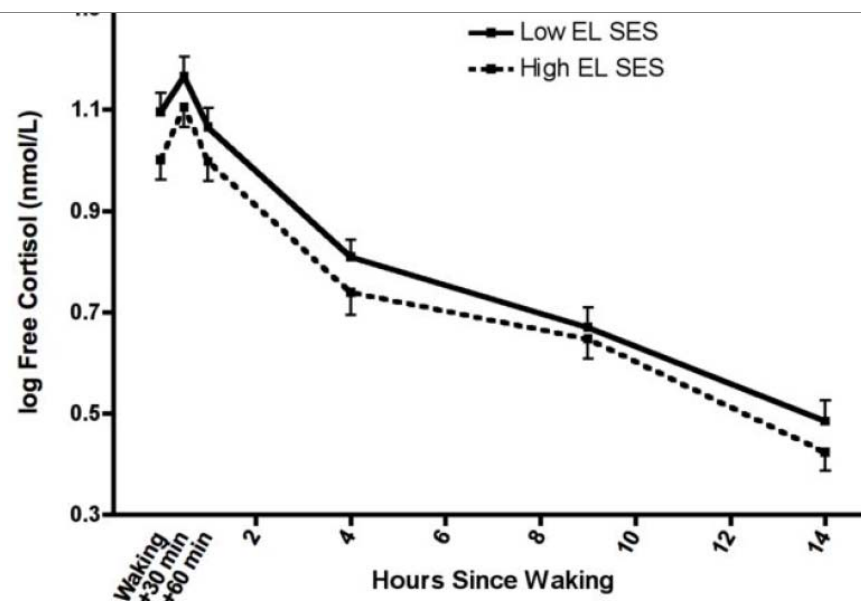
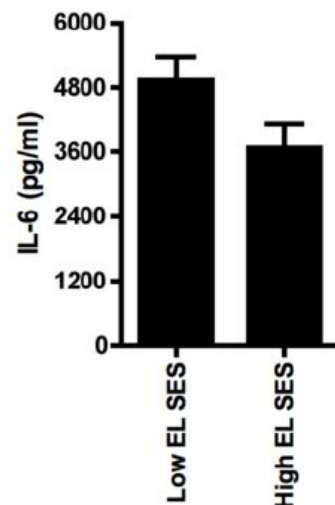
Childhood	Adulthood
Low SES	Low SES
Low SES	High SES
High SES	Low SES
High SES	High SES



(a) TLR3 Stimulation by Poly I:C

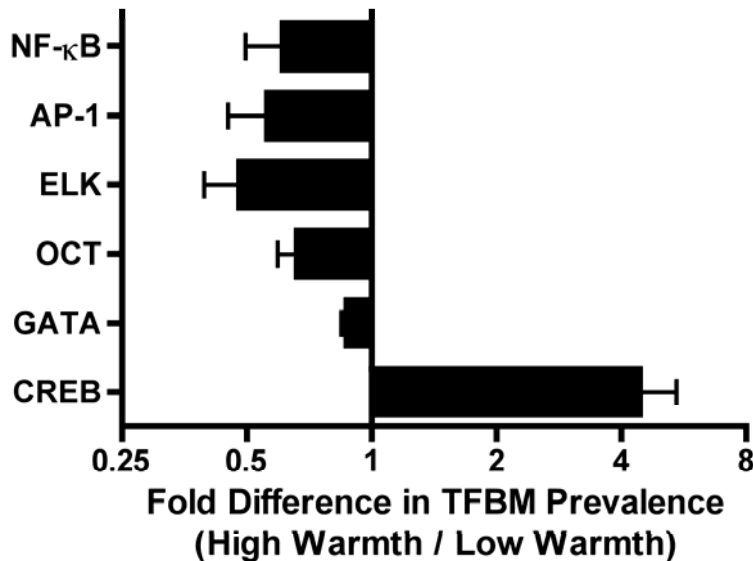
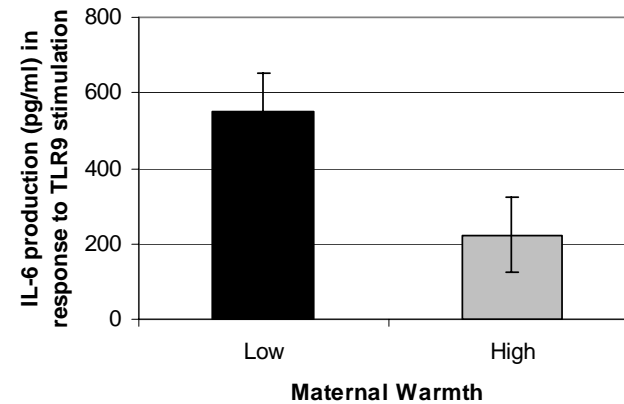
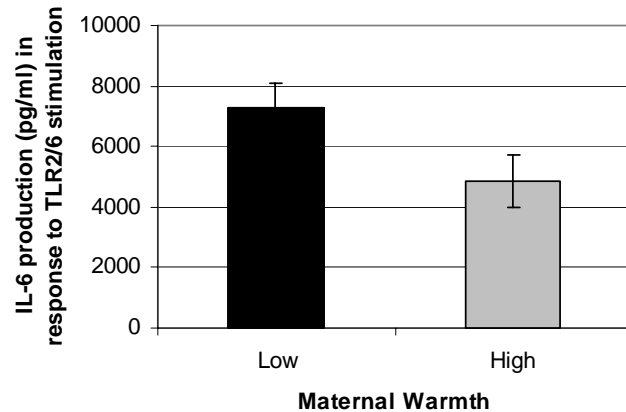


(b) TLR5 Stimulation by Flagellin



Miller et al PNAS 2009

# Maternal Warmth and Resilience of the Pro-Inflammatory Phenotype of Low Early-Life SES



# Epigenetic Vestiges of Early Parental Adversity

## Wisconsin Study of Families and Work

HCS: FDR <5%

MCS: FDR 5%-20%

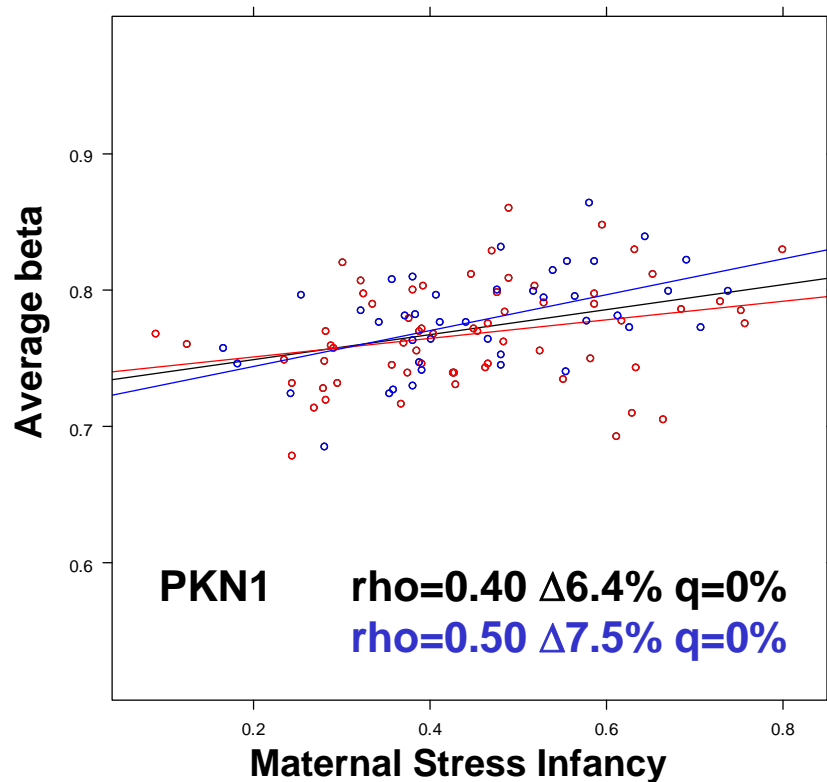
		<u>Full Group</u> (n=109)	<u>Girls</u> (n=60)	<u>Boys</u> (n=49)
<u>Infancy</u>	Maternal Stress	139 HCS	1 HCS	3 HCS
	Paternal Stress		3 HCS	
<u>Preschool</u>	Maternal Stress			
	Paternal Stress	3 HCS 29 MCS	6/9 HCS 314/1057 MCS	



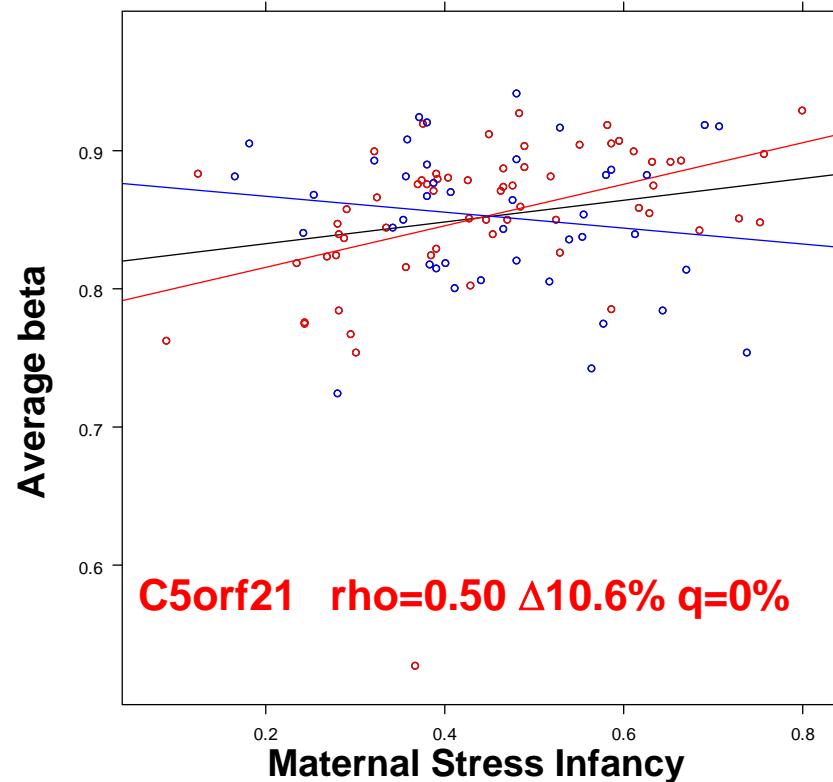
W. Thomas Boyce (Human Early Learning Partnership, UBC)  
Clyde Hertzman (Human Early Learning Partnership, UBC)  
Marilyn Essex (University of Wisconsin)

# Maternal Stress During Infancy Associated with DNA Methylation

Associated CpG site in  
full group and **boys**



**Female**-specific  
associated CpG site



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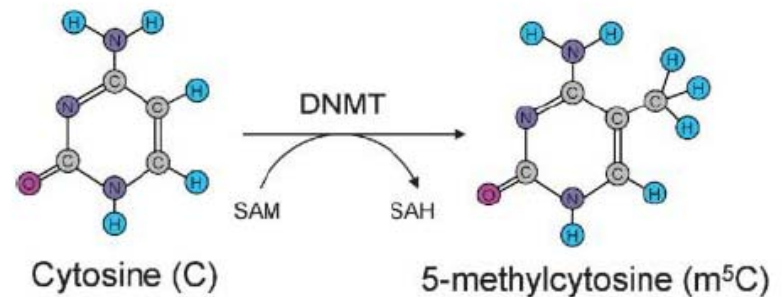
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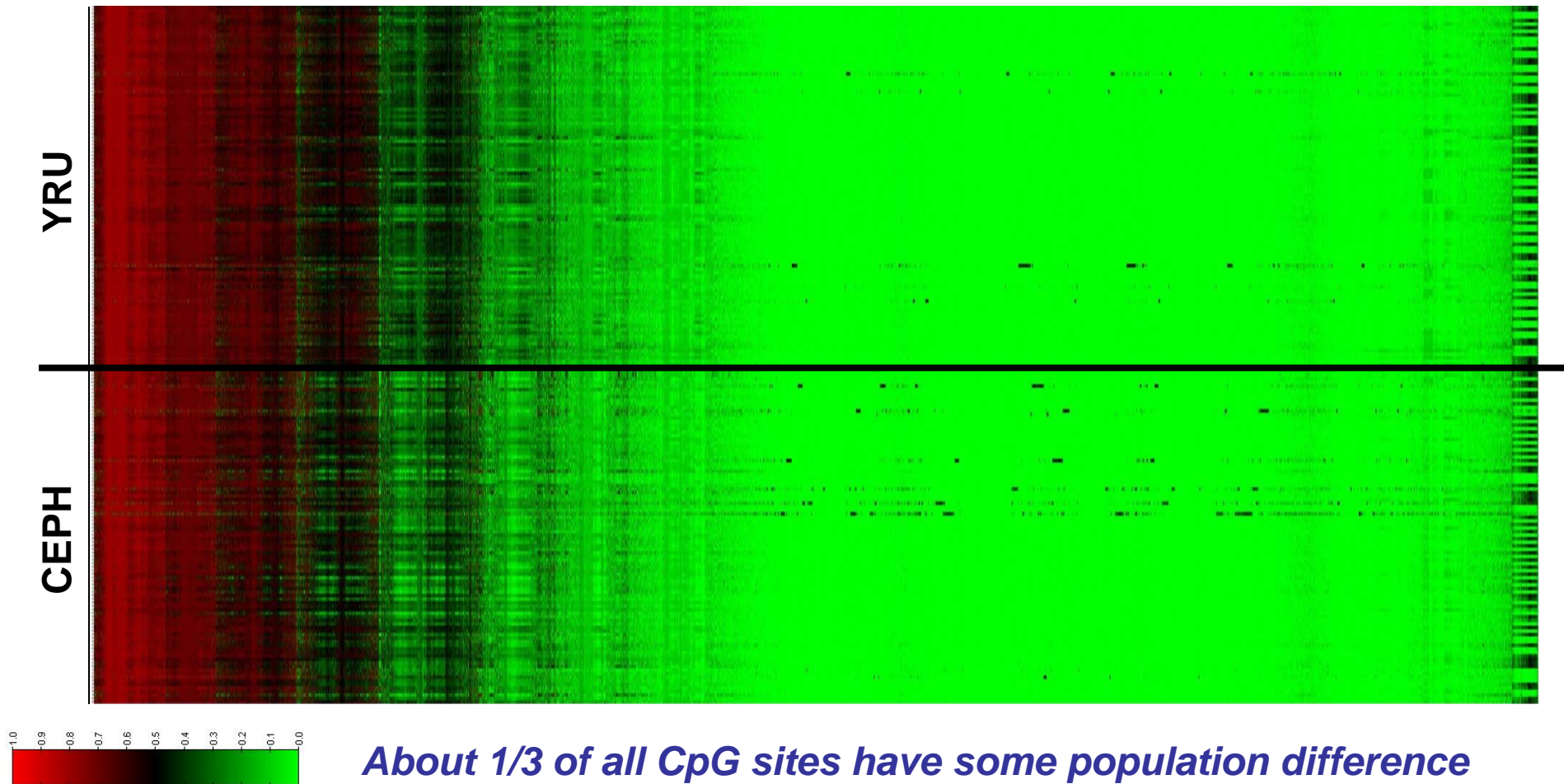




# DNA Methylation Associated with Ethnicity

Genomic DNA lymphoblastoid cell lines, 28,000 CpG sites

20 CEPH family trios (Utah, from northern European descent)  
20 Yoruban family trios (African descent)

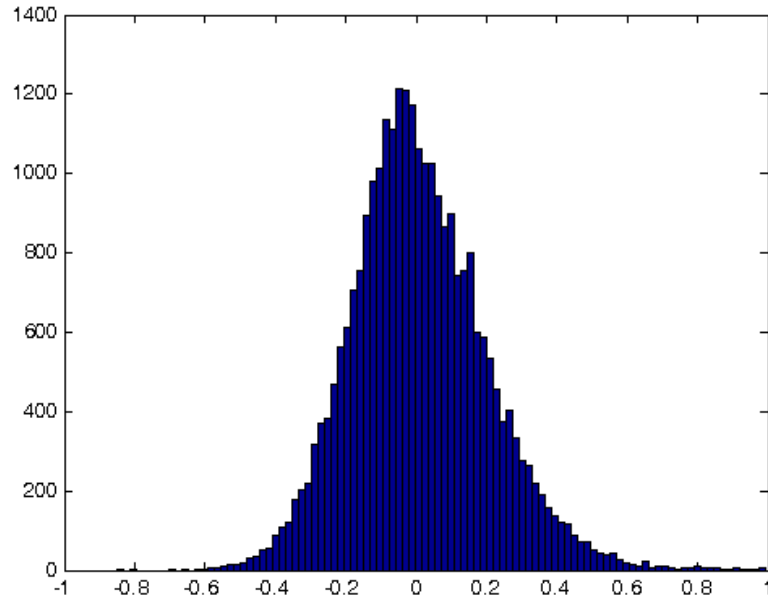


*About 1/3 of all CpG sites have some population difference*

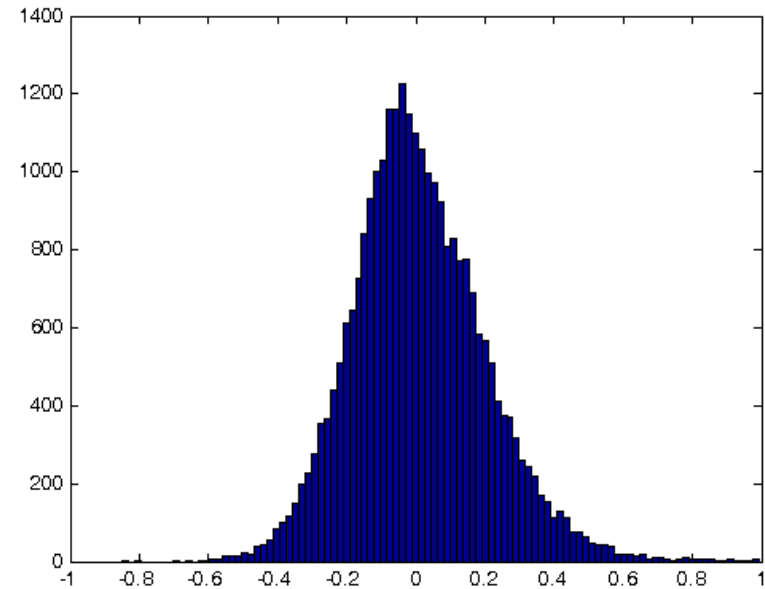


Hunter Fraser (Stanford University)

# Genetic Control of DNA Methylation



**YRI heritability (parent-child corr)**  
**2,348 sites with heritability > random**  
**(10,000 permutations)**



**CEU heritability (parent-child corr)**  
**1,986 sites with heritability > random**  
**(10,000 permutations)**

*Widespread heritability of DNA methylation affecting ~8% of CpG sites indicates genetic control of polymorphic DNA methylation*

# Summary

Epigenetics as an Integral Component of Human Health and Disease

Tissue-Specific Variation in DNA Methylation

*Aging and Lifestyle Factors Associated with DNA Methylation*

Genomic Embedding of Early Life Experiences

*Biological Residue of Early Life Poverty*

*DNA Methylation Associated with Early Life Parental Stress*

Ethnicity and Genetic Control of DNA Methylation

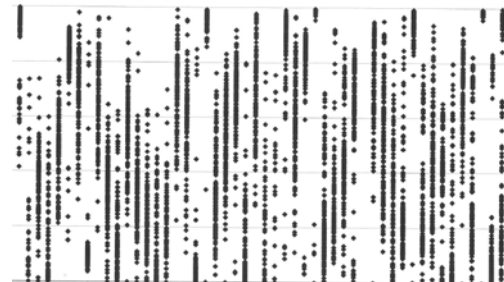
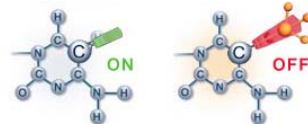
Issues to Consider:

*Robustness of DNA Methylation in Response to Environments*

*Correlation versus Causality*

*Malleability of Marks upon Intervention*

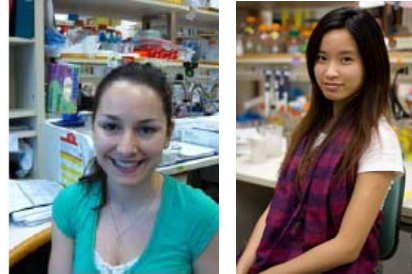
*Interplay between Genetics, Epigenetics and the Environment*



# Acknowledgements

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Dept. of Psychology, UBC**

**Hunter Fraser**

**Dept. of Biology, Stanford University**

**W. Thomas Boyce  
Clyde Hertzman  
Marilyn Essex**

**Human Early Learning Partnership, UBC  
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Dept. of Psychiatry, U of Wisconsin**

**Human Early Learning Partnership  
AllerGen NCE  
Canadian Institute for Advanced Research  
National Institutes of Health**



**BC Clinical Genomics Network (Michael Hayden)**