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DEPARTMENT OF PEDIATRICS

Developmental Origins of Chronic Disease – The Influence of Diet

Rob Waterland, PhD

waterland@bcm.edu

Food Forum
Dietary Patterns to Prevent and Manage Diet-Related Disease Across the Lifespan
Washington, DC **15 August 2023**

No conflicts of interest to disclose.

Acknowledgements

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USDA
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March of Dimes
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Cutberto Garza, MD, PhD

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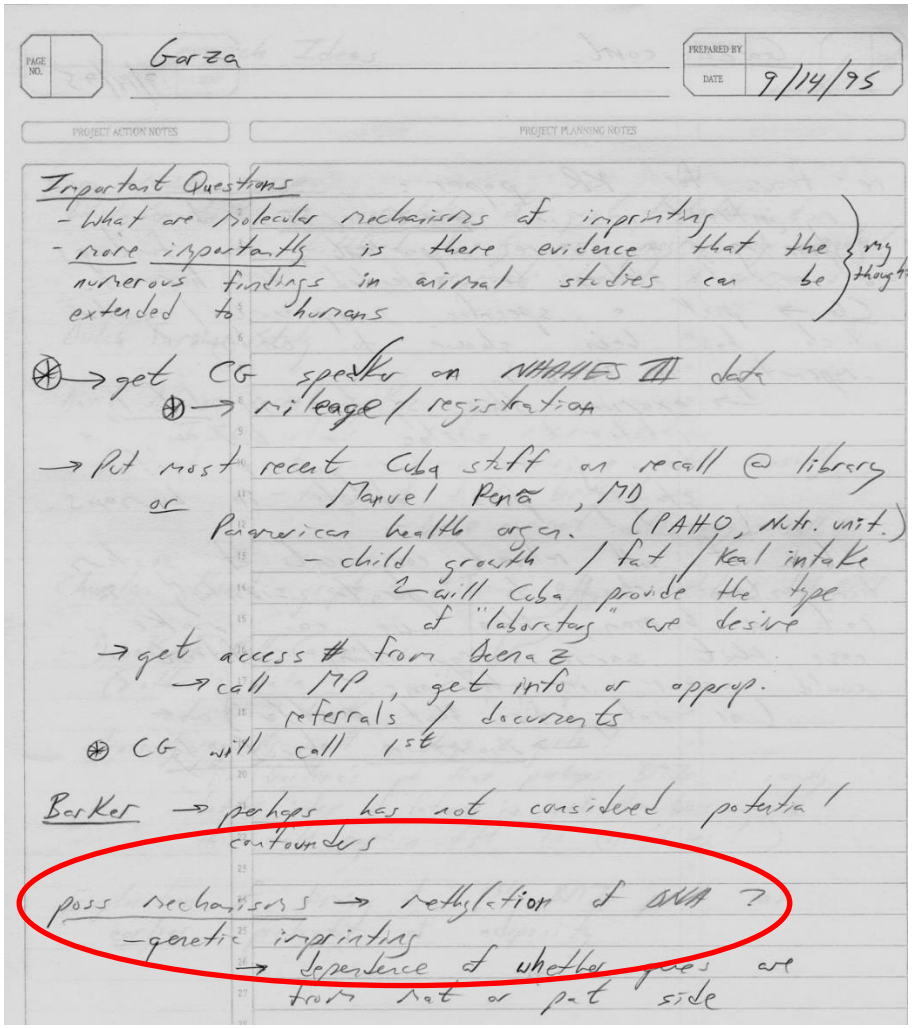


Garza

PREPARED BY

DATE 9/14/95

PROJECT ACTION NOTES

PROJECT PLANNING NOTES

Important Questions

- What are molecular mechanisms of imprinting
- more importantly is there evidence that the numerous findings in animal studies can be extended to humans

} my thoughts

⊛ → get CG spectr on NHANES III data

⊛ → mileage / registration

→ Pat most recent Cuba staff on recall @ library

or Manuel Peña, MD

Panamerican health orgn. (PAHO, Nutr. unit.)

- child growth / fat / kcal intake

2 will Cuba provide the type of "laboratory" we desire

→ get access # from Deena Z

→ call MP, get into or approp. referrals / documents

⊛ CG will call 1st

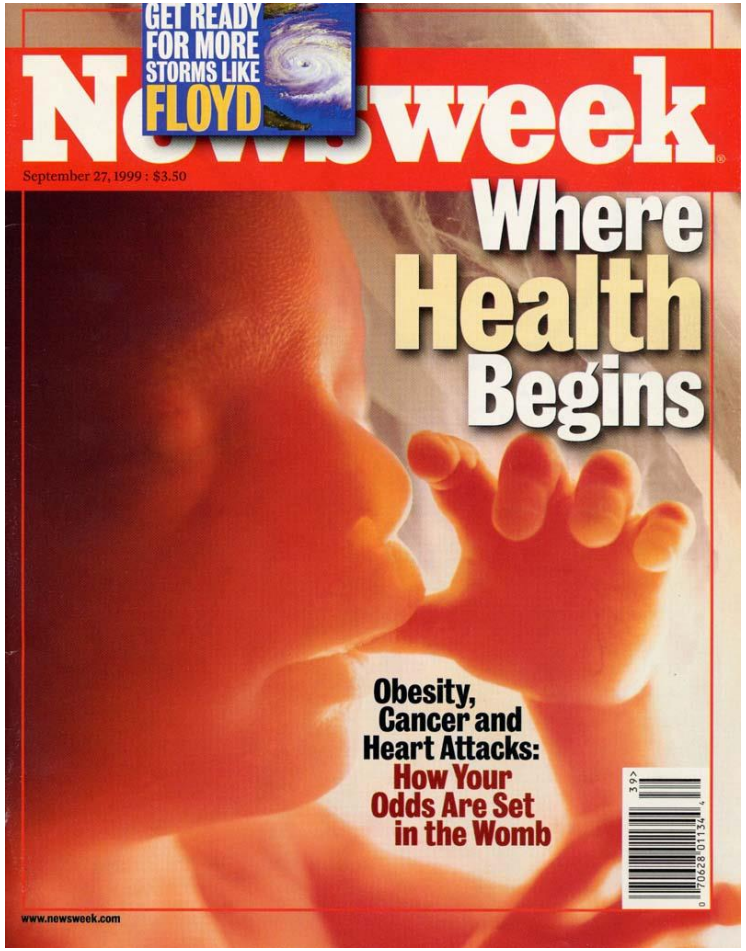
Barker → perhaps has not considered potential confounders

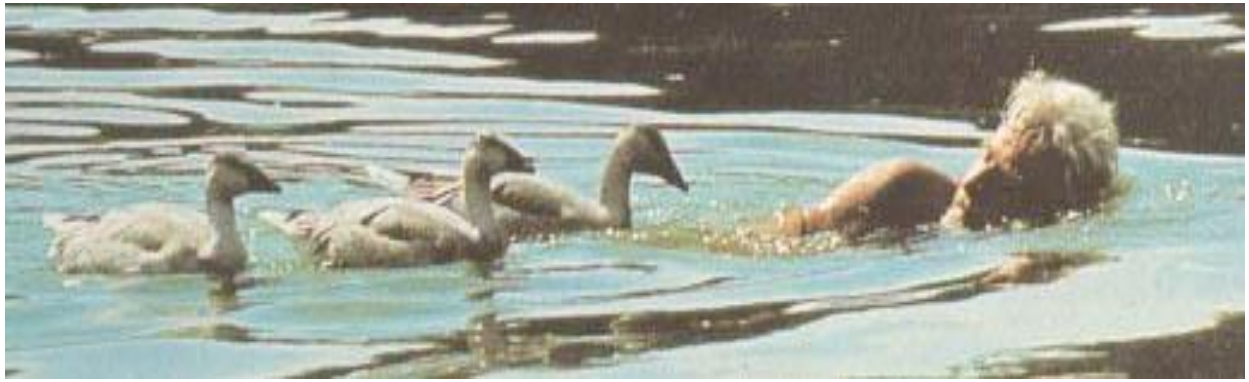
poss mechanisms → methylation of DNA ?

- genetic imprinting

→ dependence of whether genes are from Mat or Pat side

Developmental Origins of Adult Disease (DOHaD) – What are the underlying mechanisms?





Konrad Lorenz and his imprinted goslings

Metabolic Imprinting

Adaptive responses to early nutrition

Susceptibility limited to critical period of development

Persistent effect

Dose-response or threshold effect between exposure and outcome

Waterland & Garza 1999 *Am J Clin Nutr*

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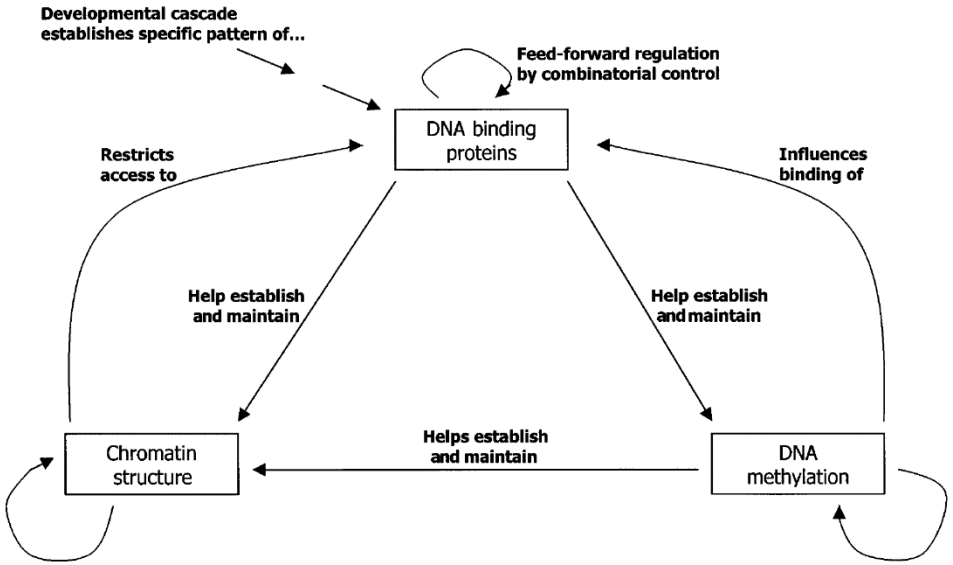
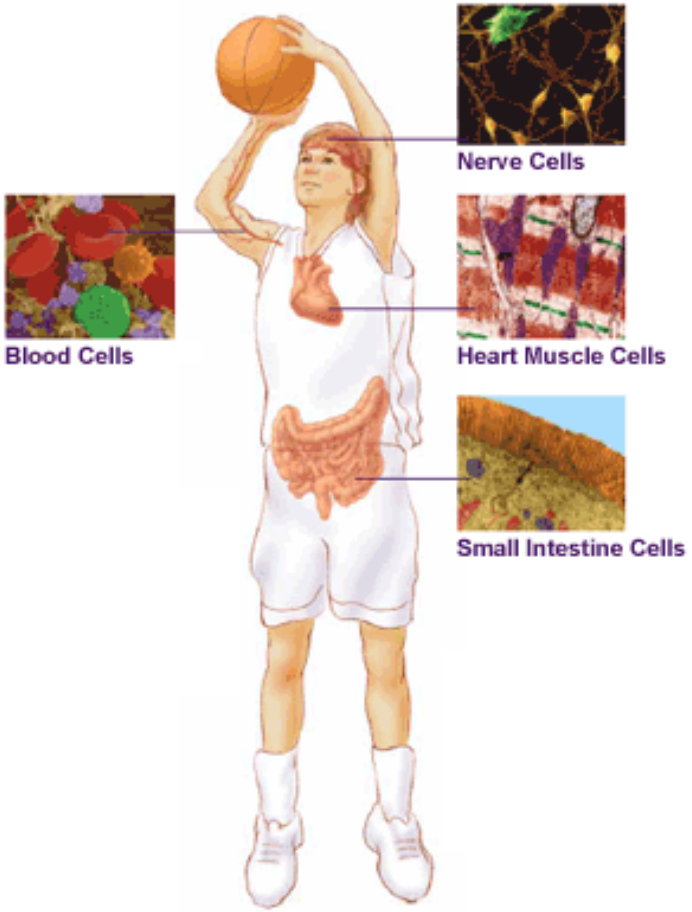
Potential Mechanisms of Metabolic Imprinting

- Induced alterations in
  - Organ structure
  - Cell number
  - Hepatocyte polyploidization
  - Clonal selection
  - Metabolic differentiation (epigenetics)

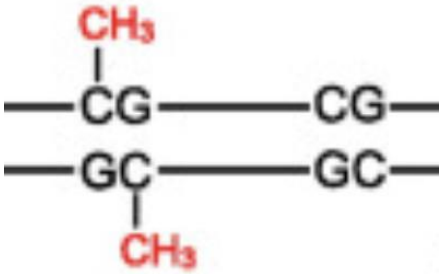


Waterland & Garza 1999 *Am J Clin Nutr*

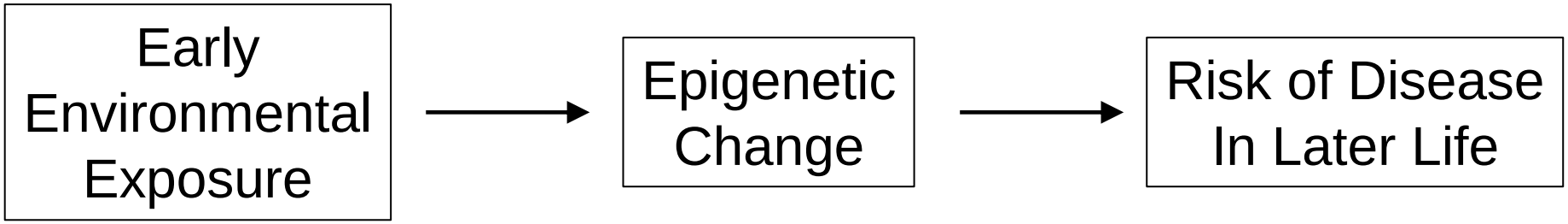
EPIGENETICS: Mitotically heritable, stable alterations in gene expression *potential* that are NOT caused by changes in DNA sequence



Our focus: DNA methylation



Epigenetic Mechanisms in DOHaD – Causal Pathway



Maternal dietary methyl supplementation before and during pregnancy alters offspring phenotype by increasing DNA methylation at metastable epialleles

- At *Agouti Viable Yellow*

- At *Axin*^{Fused}

Waterland & Jirtle 2003 *Mol Cell Biol*

Waterland et al. 2006 *Genesis*

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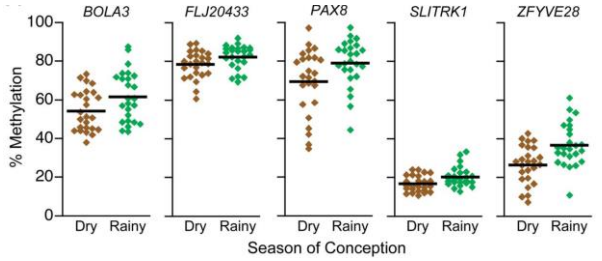
OPEN ACCESS Freely available online

PLoS GENETICS

Season of Conception in Rural Gambia Affects DNA Methylation at Putative Human Metastable Epialleles

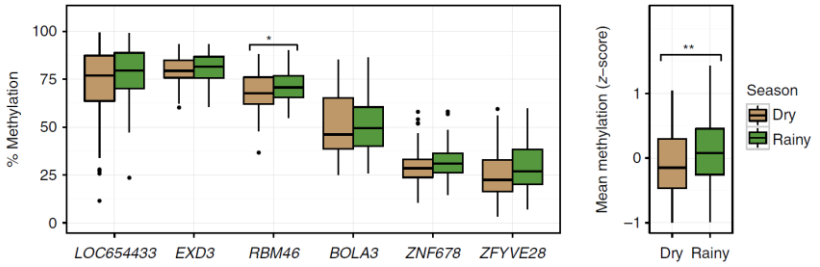
Robert A. Waterland[1,2]*, Richard Kellermayer[1], Eleonora Laritsky[1], Pura Rayco-Solon[3], R. Alan Harris[2], Michael Travisano[4], Wenjuan Zhang[1], Maria S. Torskaya[1], Jiexin Zhang[5], Lanlan Shen[1], Mark J. Manary[1], Andrew M. Prentice[3]



nature COMMUNICATIONS

Maternal nutrition at conception modulates DNA methylation of human metastable epialleles

Paula Dominguez-Salas[1], Sophie E. Moore[1], Maria S. Baker[2], Andrew W. Bergen[3], Sharon E. Cox[1], Roger A. Dyer[4], Anthony J. Fulford[1], Yongtao Guan[2,5], Eleonora Laritsky[2], Matt J. Silver[1], Gary E. Swan[6], Steven H. Zeisel[7], Sheila M. Innis[4], Robert A. Waterland[2,5], Andrew M. Prentice[1] & Branwen J. Hennig[1]

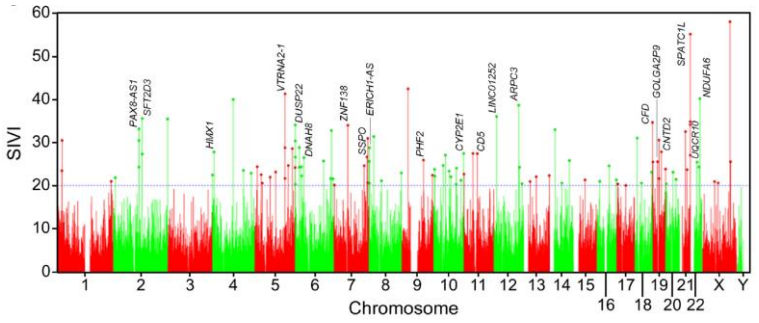


Silver *et al. Genome Biology* (2015) 16:118
DOI 10.1186/s13059-015-0660-y

Genome Biology

Independent genomewide screens identify the tumor suppressor *VTRNA2-1* as a human epiallele responsive to periconceptional environment

Matt J Silver[1,2†], Noah J Kessler[3†], Branwen J Hennig[1,2], Paula Dominguez-Salas[4,5], Eleonora Laritsky[3], Maria S Baker[3], Cristian Coarfa[6], Hector Hernandez-Vargas[7], Jovita M Castelino[8], Michael N Routledge[8], Yun Yun Gong[9], Zdenko Herceg[7], Yong Sun Lee[10], Kwanbok Lee[10], Sophie E Moore[1,2,11], Anthony J Fulford[1,2], Andrew M Prentice[1,2*] and Robert A Waterland[3,12*]



Waterland et al 2010 *PLoS Genetics*
Dominguez-Salas et al 2014 *Nat Commun*
Silver and Kessler et al 2015 *Genome Biol*

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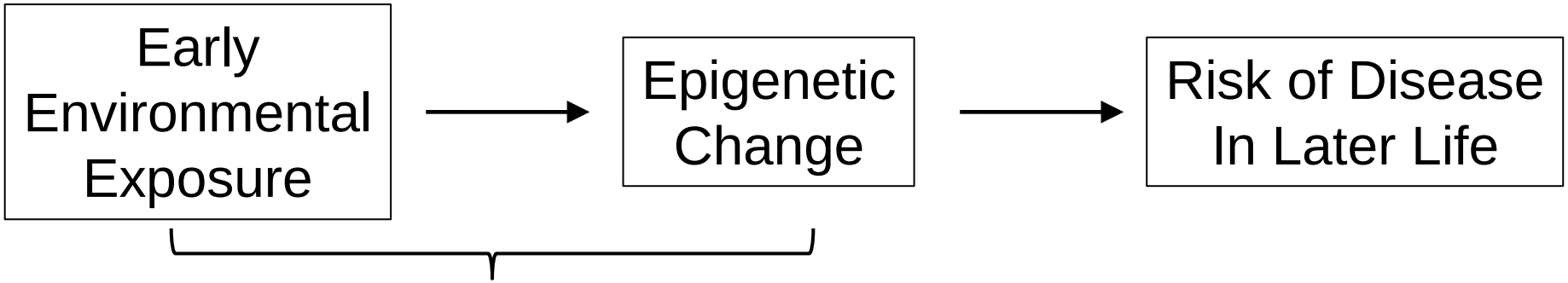
In Humans, at Metastable Epialleles/CoRSIVs, first step of pathway is well established

Epigenetic Mechanisms in DOHaD – Causal Pathway



Evidence at Metastable Epialleles/CoRSIVs

- Periconceptional nutrition in The Gambia (Waterland/Prentice et al. 2010, 2014, 2015, 2018, 2019)
- Assisted reproductive technology (ART) Estill et al. 2016 *Fert Steril*
- Early famine exposure (Bangladesh) Finer et al. 2016 *BMJ Open*
- Prenatal perfluoroalkyl exposure (Japan) Miura et al. 2018 *Environment Intl*.

Epigenetic Epidemiology – Well Known Obstacles

- Epigenetic regulation is generally cell-type specific

- Reverse causality
  - Epigenetic changes associated with disease may be causes – or consequences – of the disease

Waterland & Michels 2007 *Ann Rev Nutr*

Systemic Interindividual Variation in DNA Methylation Circumvents Both Obstacles

- DNA methylation in blood is an indication of epigenetic regulation throughout the body

- Methylation is established in the very early embryo and stable thereafter

Waterland & Michels 2007 *Ann Rev Nutr*

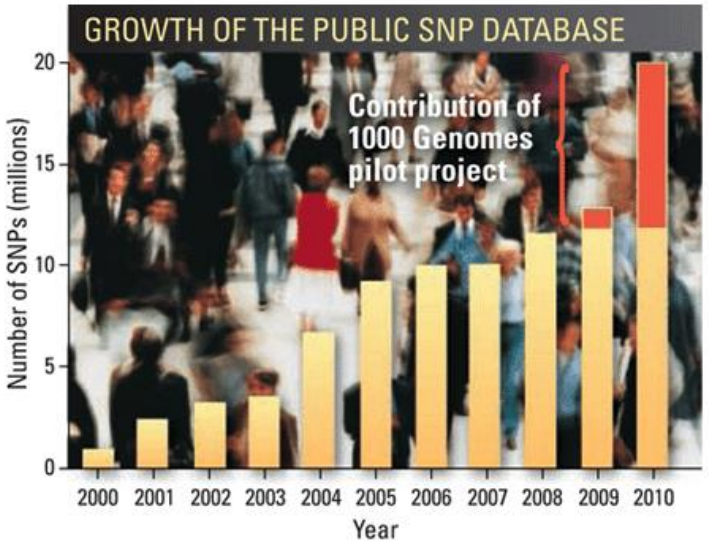
We recently reported another important but less recognized obstacle

Forbes.com

To Launch the GWAS Era, the First Step was to Map Common Sequence Variants

- 2001 - First draft human genome published
- 2002 – International HapMap Project launched
- 2008 – 1000 Genomes Project launched

"… *the HapMap will characterize… the 0.1% (of the genome) where we differ from each other*."



The International HapMap Consortium 2003 *Nature*

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But, So Far, No ‘Epi-HapMap’ Project

- Instead, epigenetic epidemiologists relied upon methylation microarrays by Illumina
  - 2011 – HM450 array (450,000 probes), designed to cover
    - 99% of RefSeq genes, and 96% of CpG islands
  - 2016 – EPIC array (850,000 probes), designed to cover
    - >90% of probes on HM450 array, 58% of FANTOM5 enhancers, and additional regulatory elements

Bibikova et al. 2011 *Genomics*
Pidsley et al. 2016 *Genome Biol*

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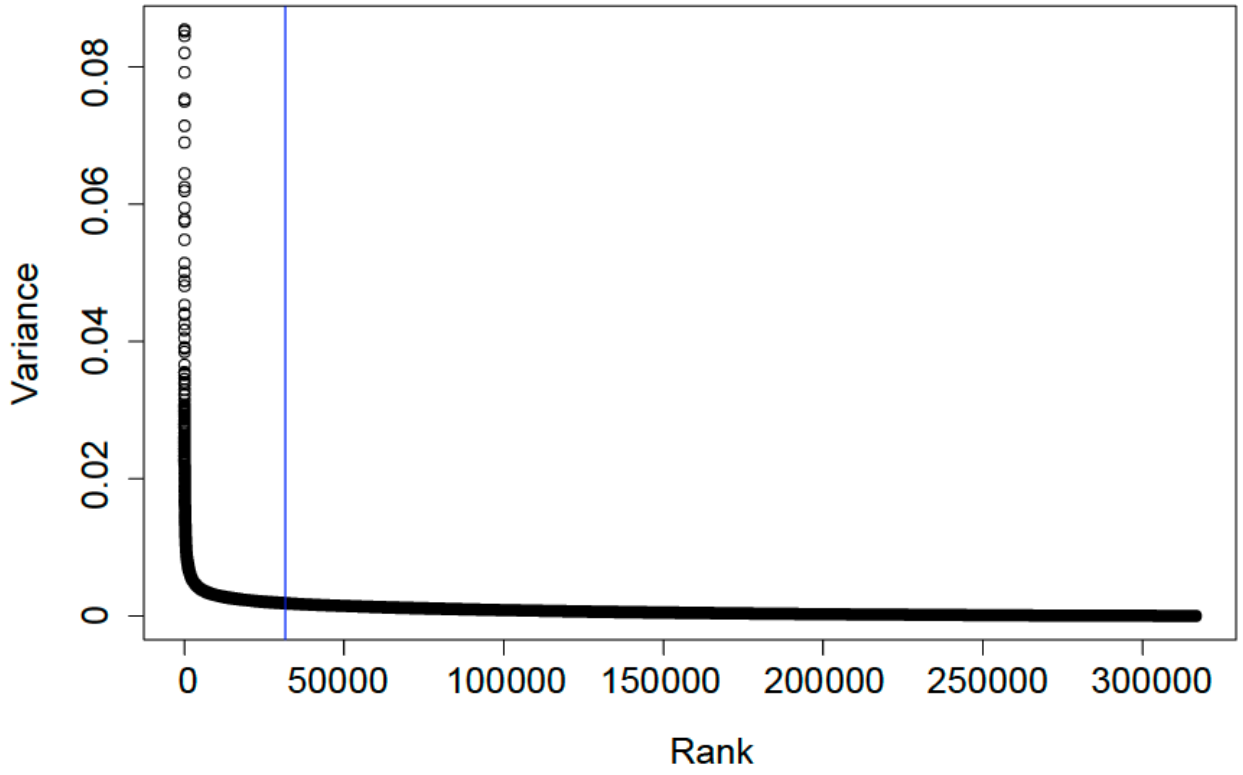
- Unfortunately, ~95% of the probes show negligible interindividual variation in normal somatic tissue

Bibikova et al. 2011 *Genomics*
Pidsley et al. 2016 *Genome Biol*

Most HM450 and EPIC Probes Show Negligible Interindividual Variance

HM450 – Adipose tissue of 648 women



Grundberg et al. 2013 *Am J Hum Genet*

Without Interindividual Variation, Epigenetic Epidemiology is Impossible

Epigenetic epidemiology: The study of the associations between interindividual epigenetic variation and risk of disease

Waterland & Michels 2007 *Ann Rev Nutr*

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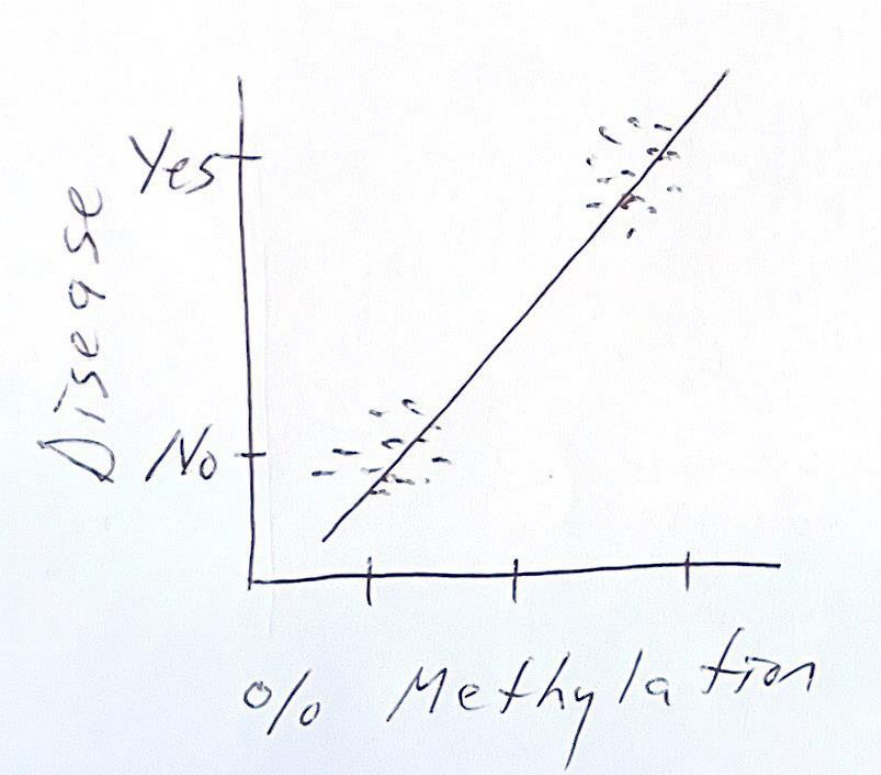
Why Is Interindividual Variation Crucial?



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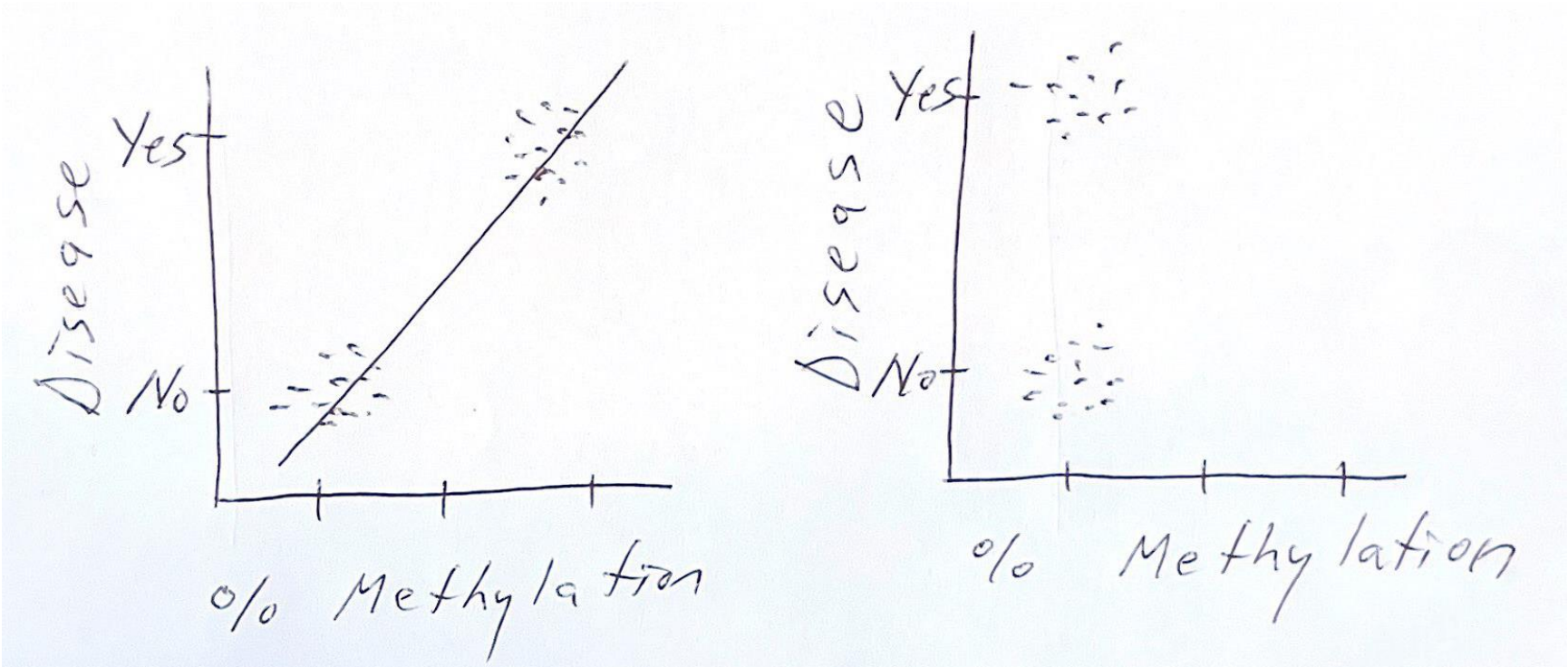
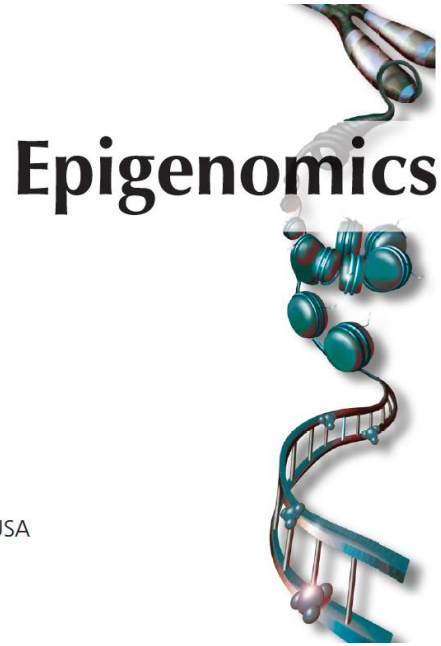


Editorial



A new era for epigenetic epidemiology

Chathura J Gunasekara[1] & Robert A Waterland*,[1,2]

[1]USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA

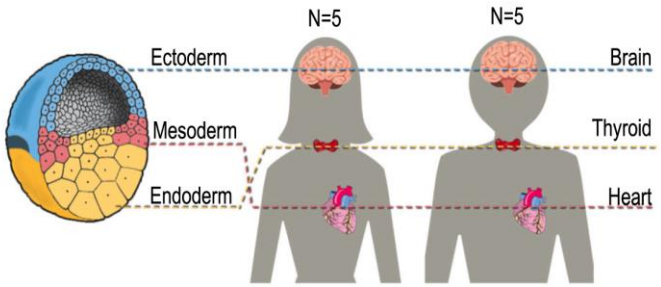
[2]Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA

*Author for correspondence: waterland@bcm.edu

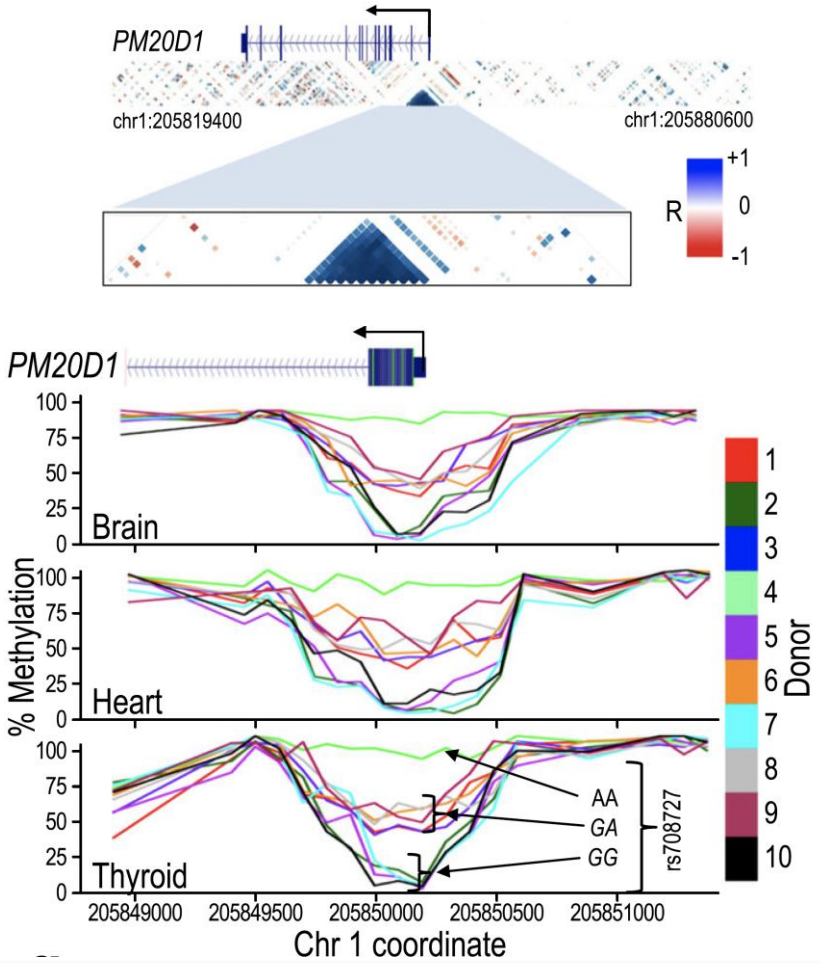
How did this problem come to our attention?

In 2019 we reported ~10,000 correlated regions of systemic interindividual epigenetic variation (CoRSIVs) in humans

Studied 10 GTEx donors



Example of a CoRSIV at the *PM20D1* promoter



Gunasekara et al 2019 *Genome Biol*

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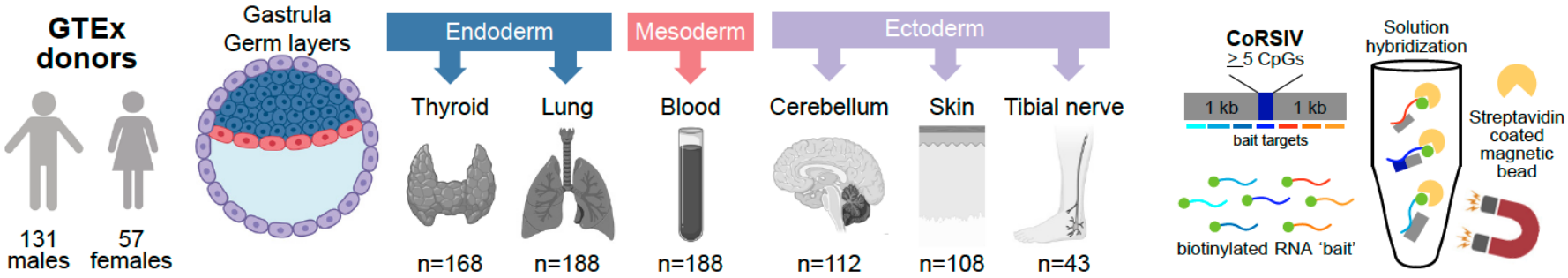
We set out to validate CoRSIVs in a larger number of individuals.

Studying Multiple Tissues of 188 GTEx Donors Validates CoRSIVs



- Validated systemic interindividual variation.

- Assessment of genetic influences on CoRSIV methylation (mQTL) yielded the biggest surprise.

Gunasekara et al 2023 *Genome Biol*

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The Genetics of DNA Methylation Consortium (GoDMC) analyzed HM450 data on >30,000 people

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-021-00923-x

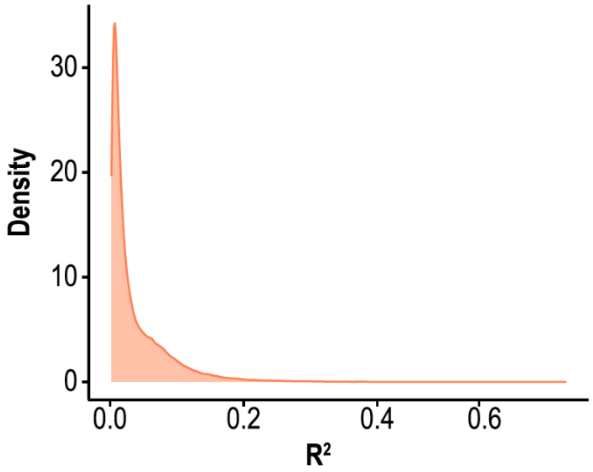
Check for updates

Genomic and phenotypic insights from an atlas of genetic effects on DNA methylation

Min et al 2021 *Nat Genet*

We Compared our mQTL Results with Those of GoDMC

GoDMC HM450 mQTL



Min et al 2021 *Nat Genet*
Gunasekara et al 2023 *Genome Biol*

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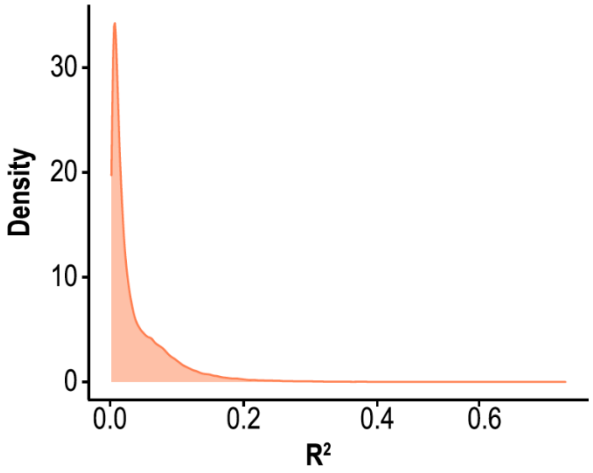
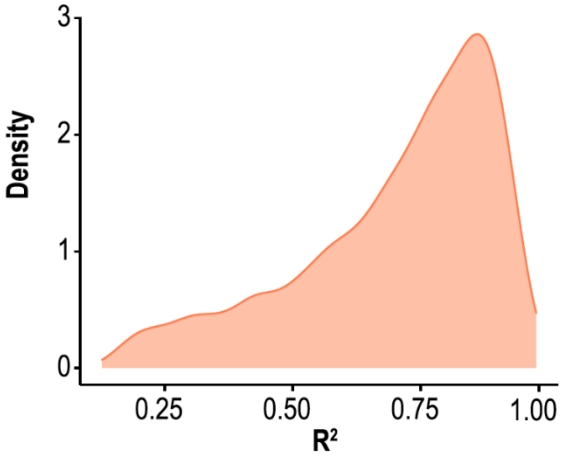
We Discovered *70-Fold* More Genetic Influence on Human Methylation Than Ever Detected

GoDMC HM450 mQTL



GTEx CoRSIV mQTL



Min et al 2021 *Nat Genet*
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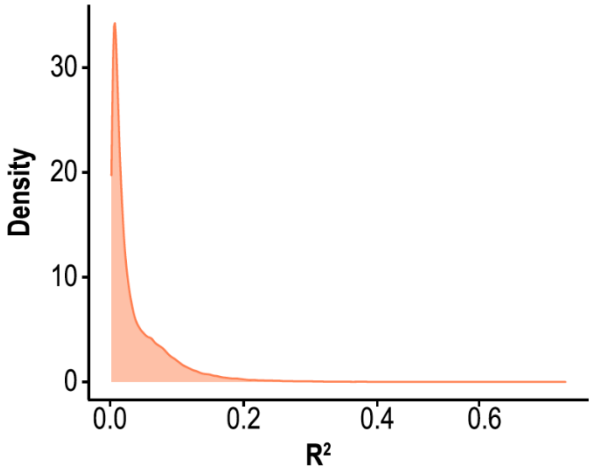
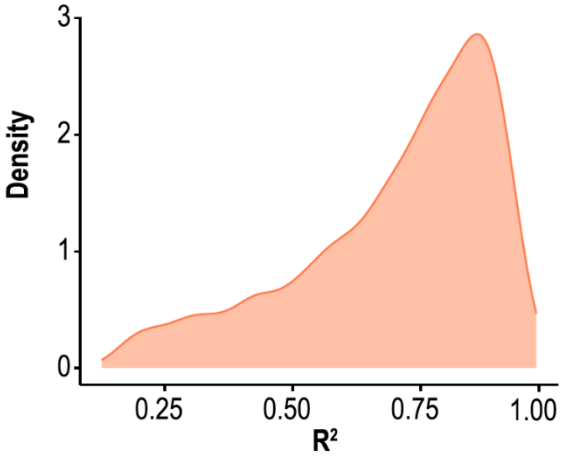
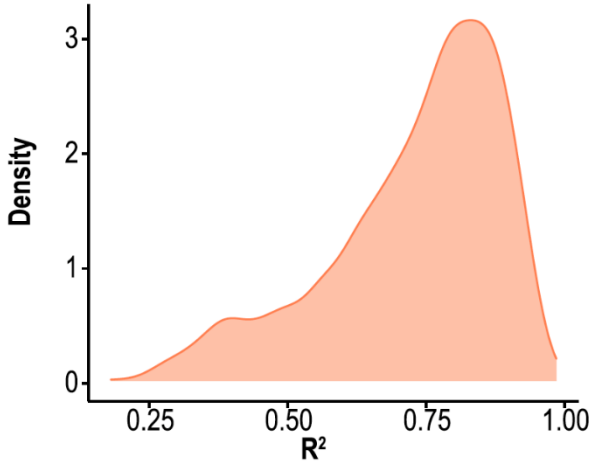


GTEx CoRSIV mQTL



USC CoRSIV mQTL



Min et al 2021 *Nat Genet*
Gunasekara et al 2023 *Genome Biol*

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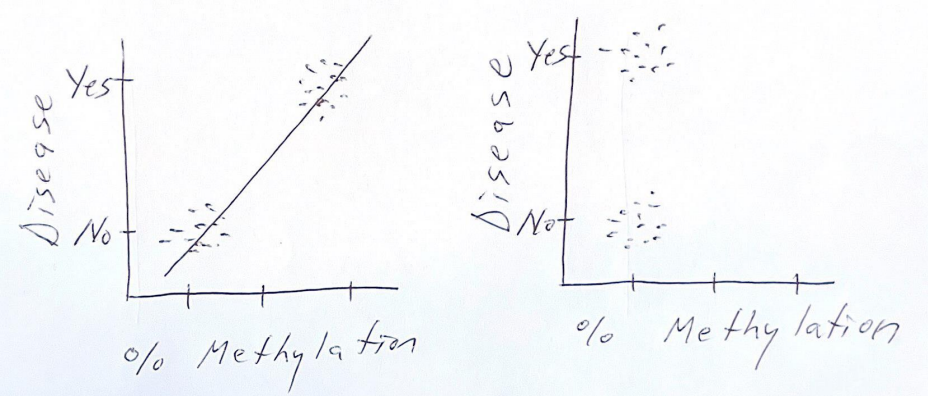
How is this relevant to epigenetic epidemiology?

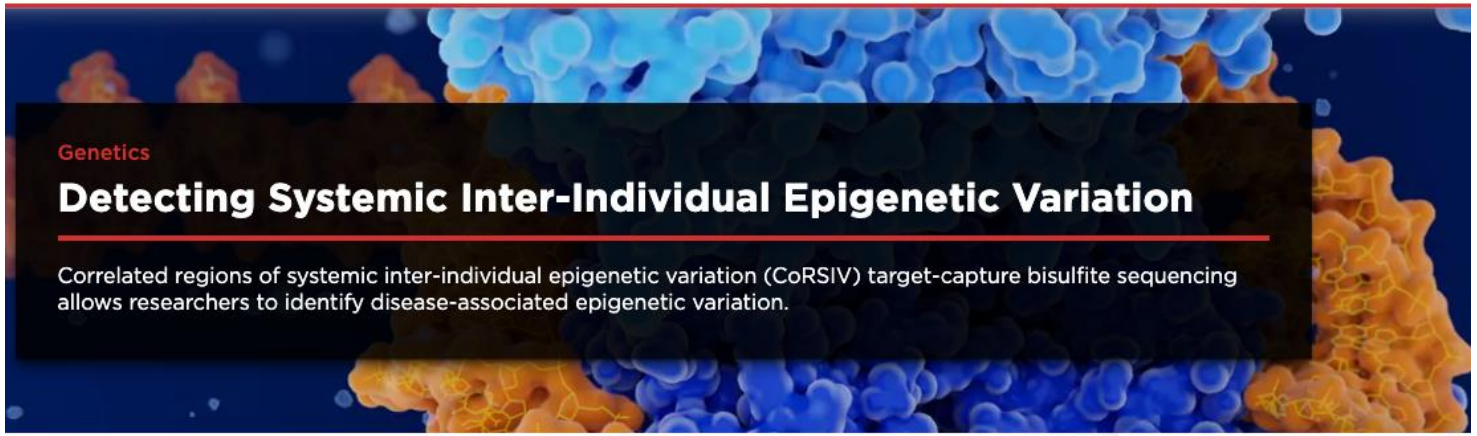
Interindividual variation is essential for not only mQTL, but also epigenetic epidemiology



- A focus on interindividual variants will improve the ability to detect associations with disease.
- 90% of known CoRSIVs are not covered by the Illumina arrays.
  - <1% of probes are within CoRSIVs, but these are often top hits in published EWAS.

Gunasekara & Waterland 2019 *Epigenomics*
Gunasekara et al 2023 *Genome Biol*

Somebody needs to develop a commercial platform for the study of CoRSIVs!



Genetics

Detecting Systemic Inter-Individual Epigenetic Variation

Correlated regions of systemic inter-individual epigenetic variation (CoRSIV) target-capture bisulfite sequencing allows researchers to identify disease-associated epigenetic variation.

Epigenetic epidemiology is rising in popularity, but the field presents technical challenges not found in genetic epidemiology. DNA methylation is often cell type-specific, making it difficult to epigenotype an individual using peripheral blood DNA. However, correlated regions of systemic inter-individual epigenetic variation (CoRSIV) target-capture bisulfite sequencing allows researchers to use easily biopsied tissues such as peripheral blood to study systemic epigenetic differences among individuals and identify disease-associated epigenetic variation.

Download this application note from Agilent Technologies to learn more about how researchers use CoRSIV panels to assay SIVs in large population studies and discover associations with human diseases.

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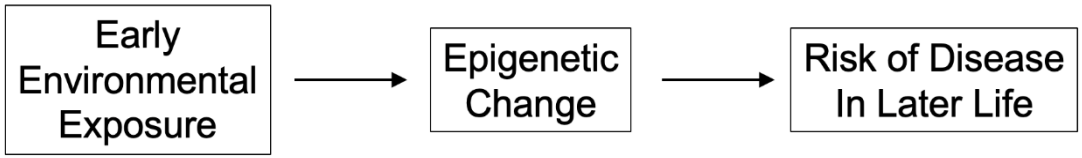
representative by telephone c

Time for a Fresh Start

- The Illumina methylation platform has handicapped the field of epigenetic epidemiology
- CoRSIVs are a logical focus for DOHaD
  - Stable and systemic interindividual variants
    - Measurements in blood are relevant to any tissue
    - Establishment of methylation is sensitive to early environment



- We have developed and validated a technology to study human CoRSIVs at the population level
  - Commercially available from Agilent

waterland@bcm.edu