Does DNA Methylation Facilitate Genome Diversity and Phenotypic Plasticity in Marine Invertebrates?

Steven Roberts
Associate Professor
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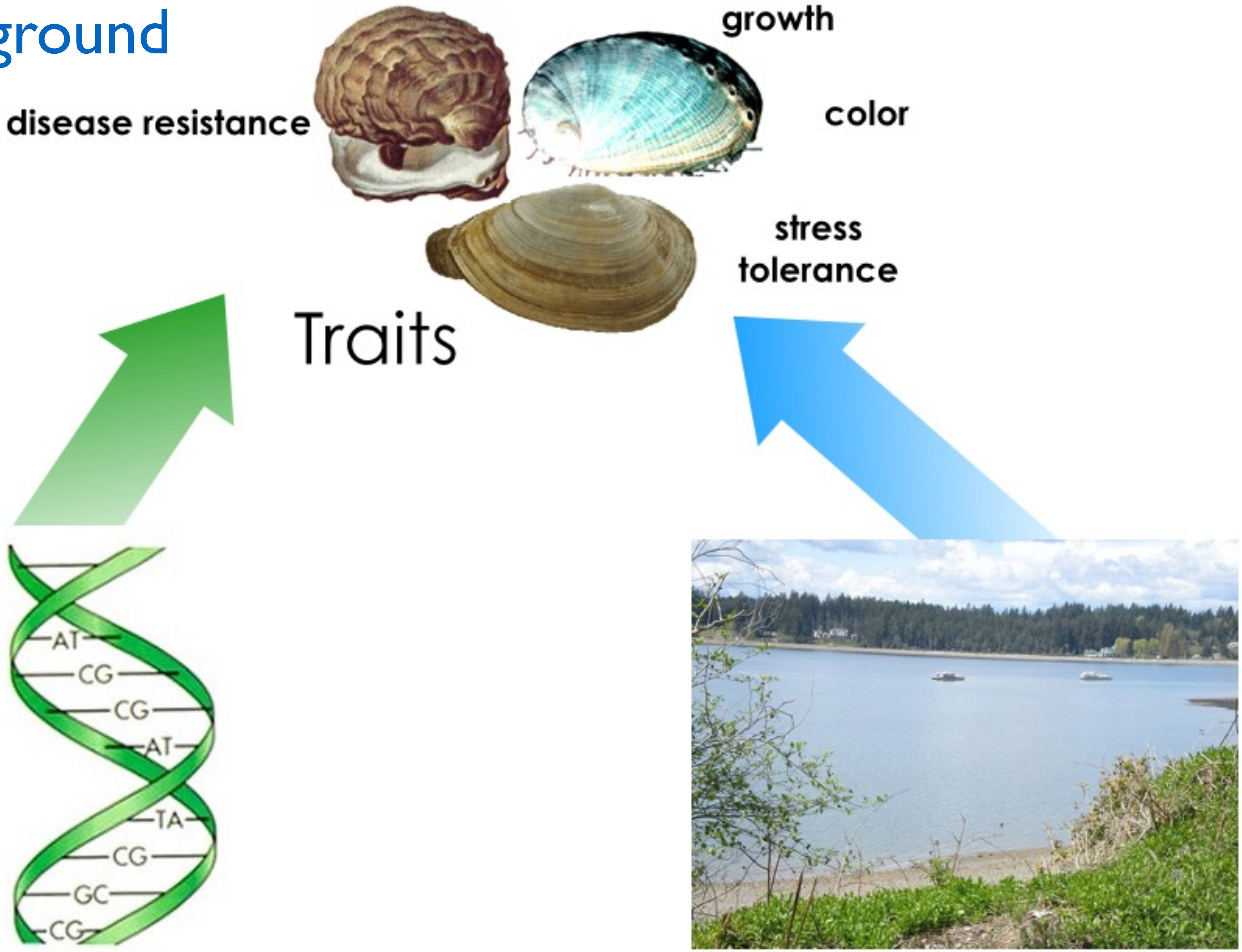
Background



disease resistance

growth

color

stress tolerance

Traits

Background

disease resistance

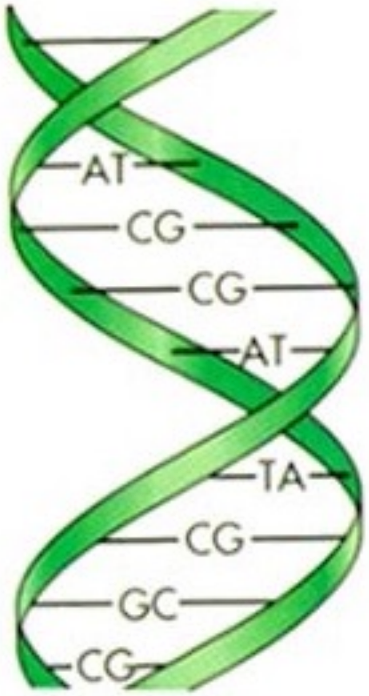
growth

color

stress tolerance

Traits

Transcriptome



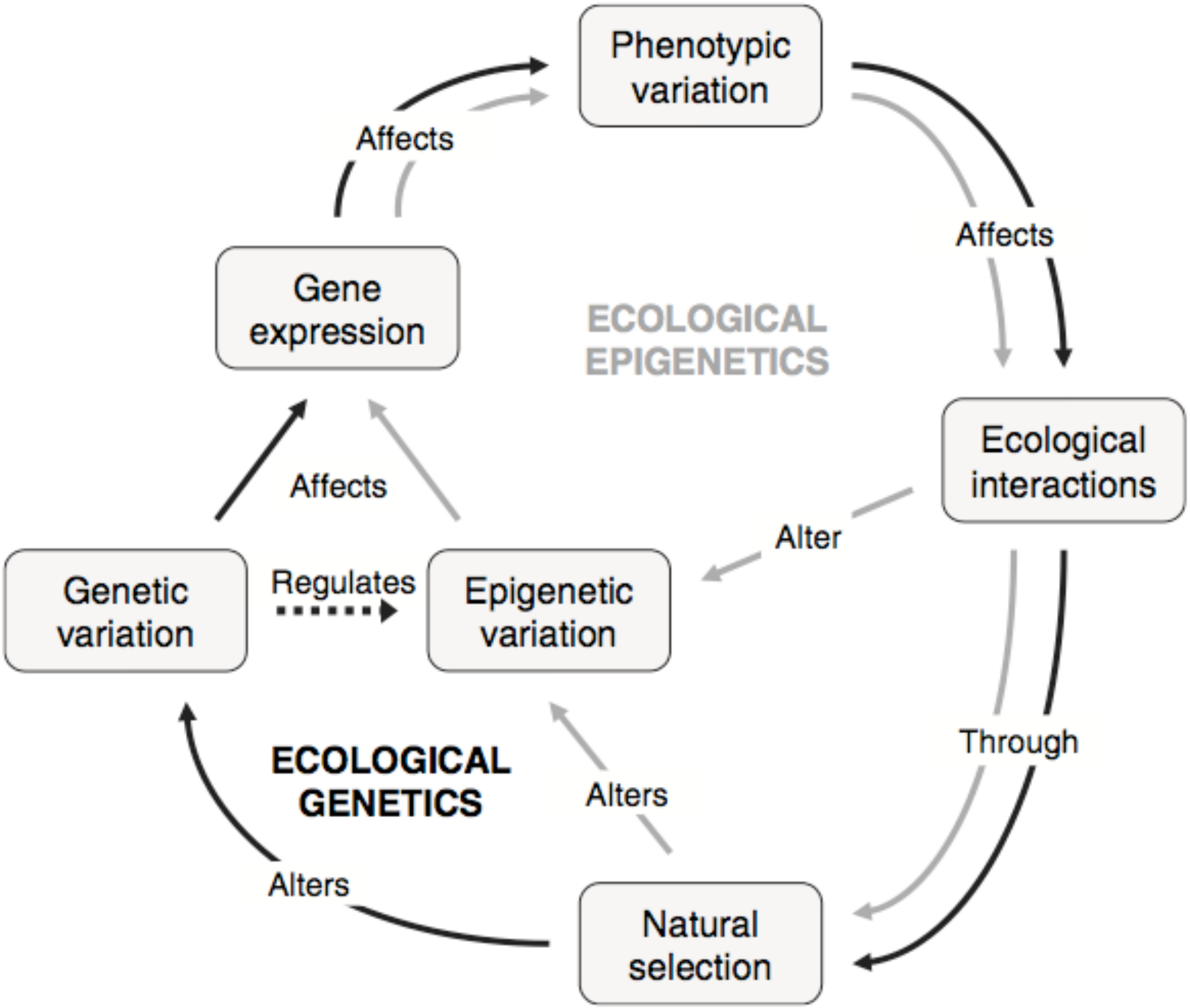
Background

disease resistance

growth

Traits

Epigenetics



Phenotypic variation

Affects

Ecological interactions

Affects

Gene expression

ECOLOGICAL EPIGENETICS

Affects

Alter

Genetic variation

Regulates

Epigenetic variation

ECOLOGICAL GENETICS

Alters

Through

Alters

Natural selection

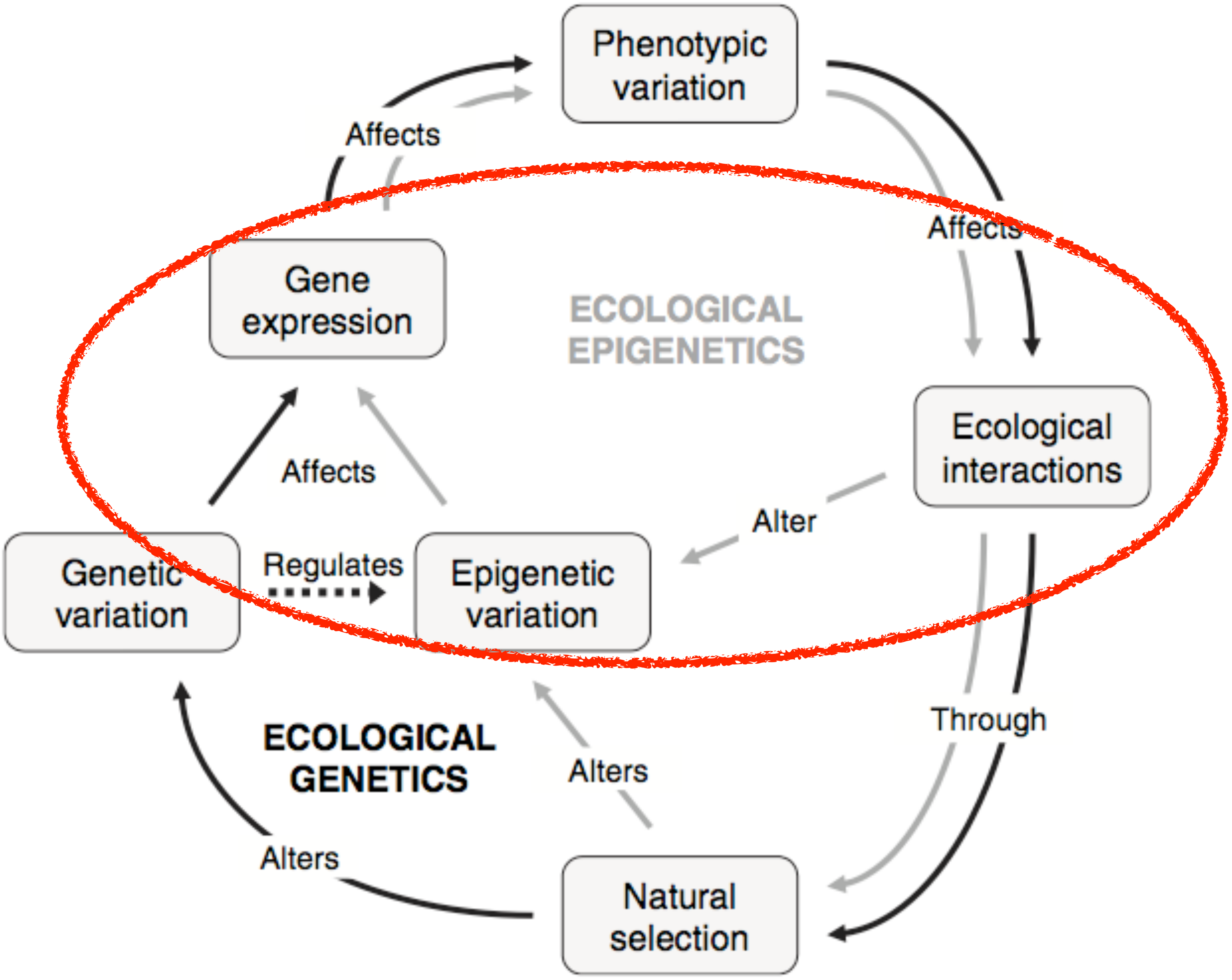
modified from

Ecology Letters, (2008) **11**: 106–115 doi: 10.1111/j.1461-0248.2007.01130.x

IDEA AND PERSPECTIVE

Epigenetics for ecologists

Oliver Bossdorf,[1]* Christina L. Richards[2] and Massimo Pigliucci[3]



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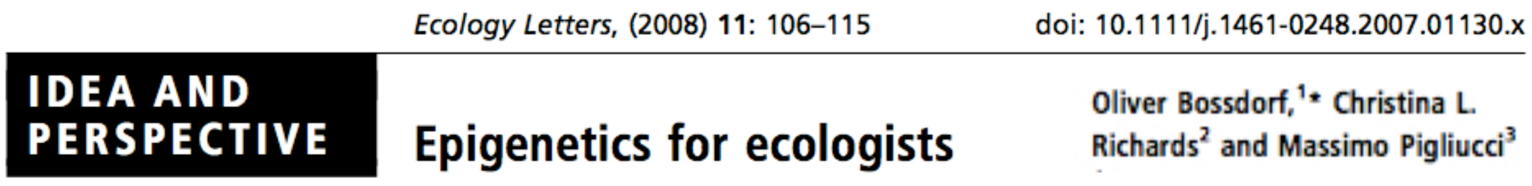

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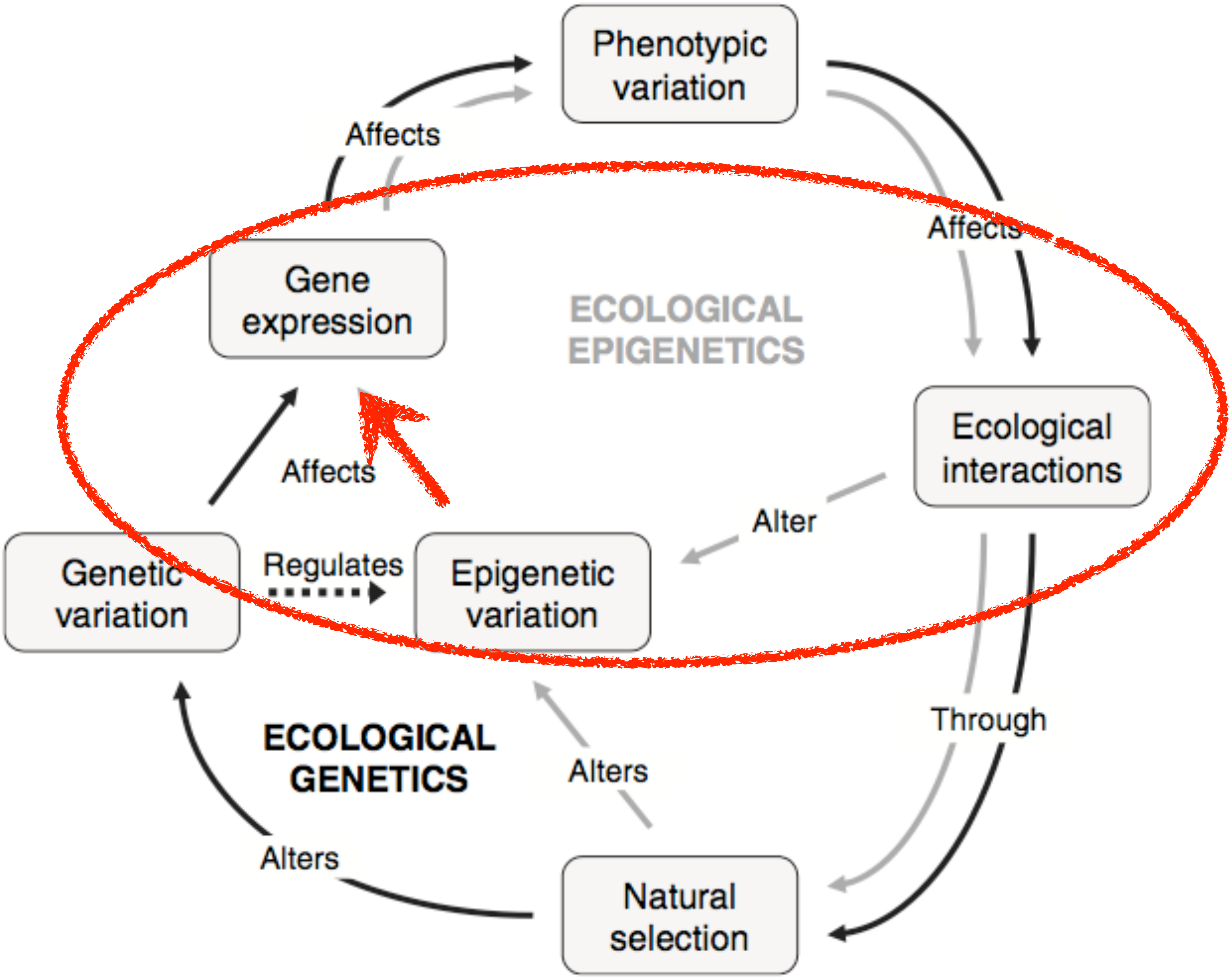

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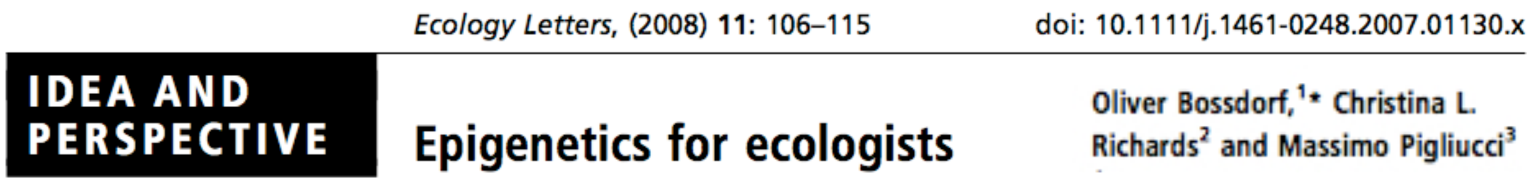
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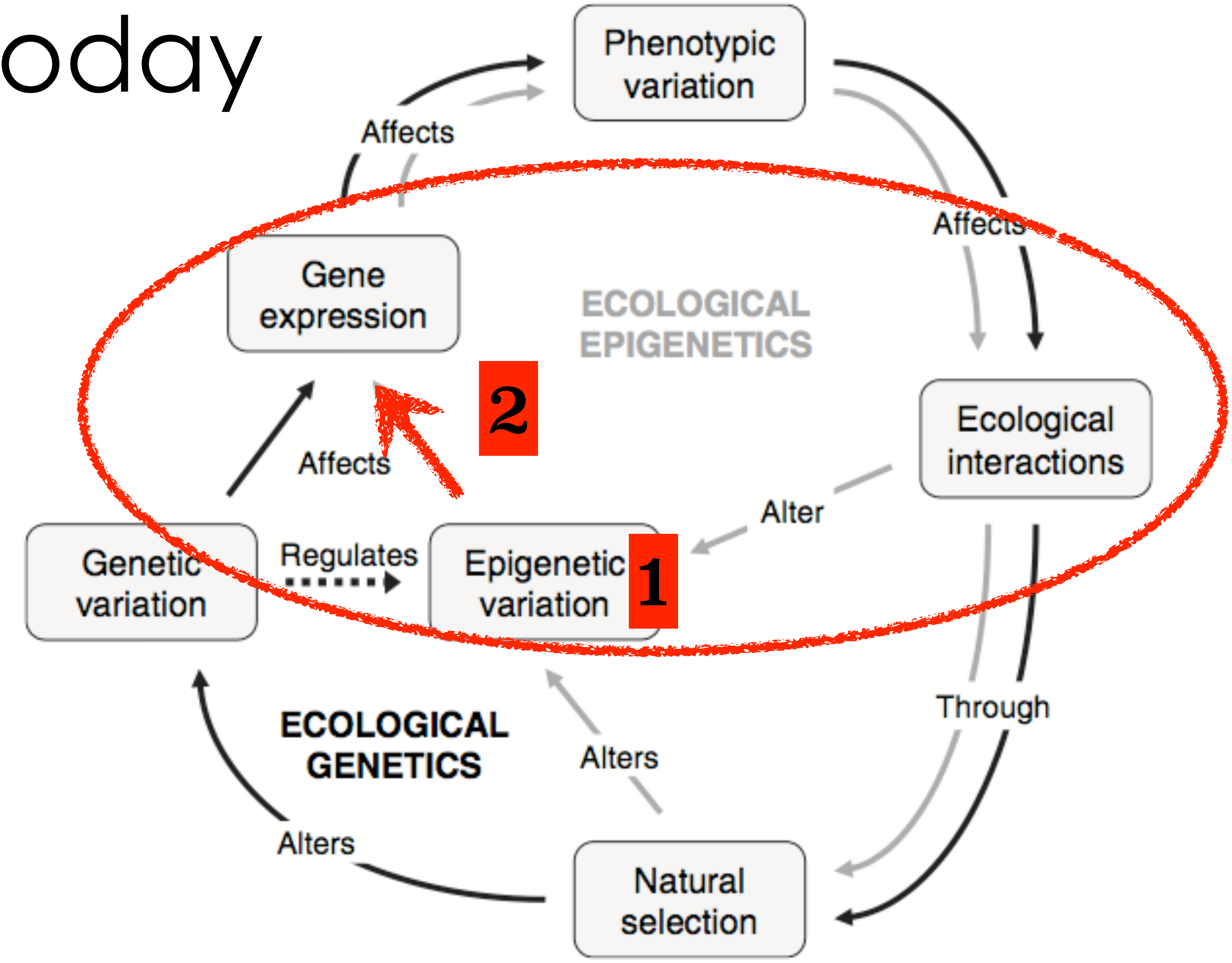

Phenotypic variation

Affects

Gene expression

ECOLOGICAL EPIGENETICS

2

Affects

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1

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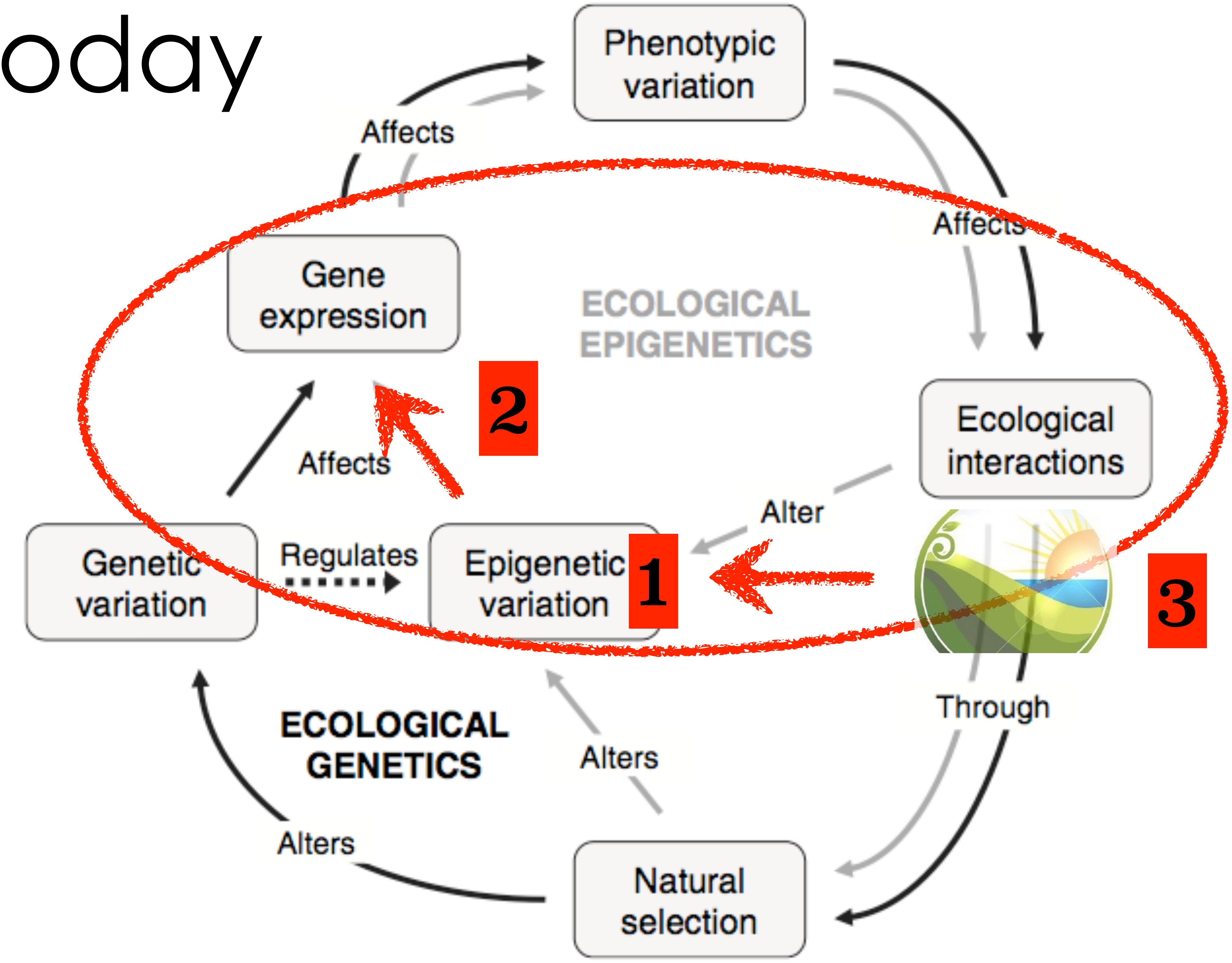

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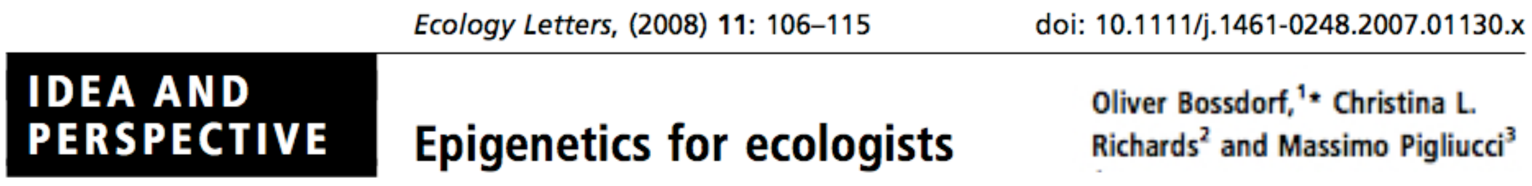
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IDEA AND PERSPECTIVE

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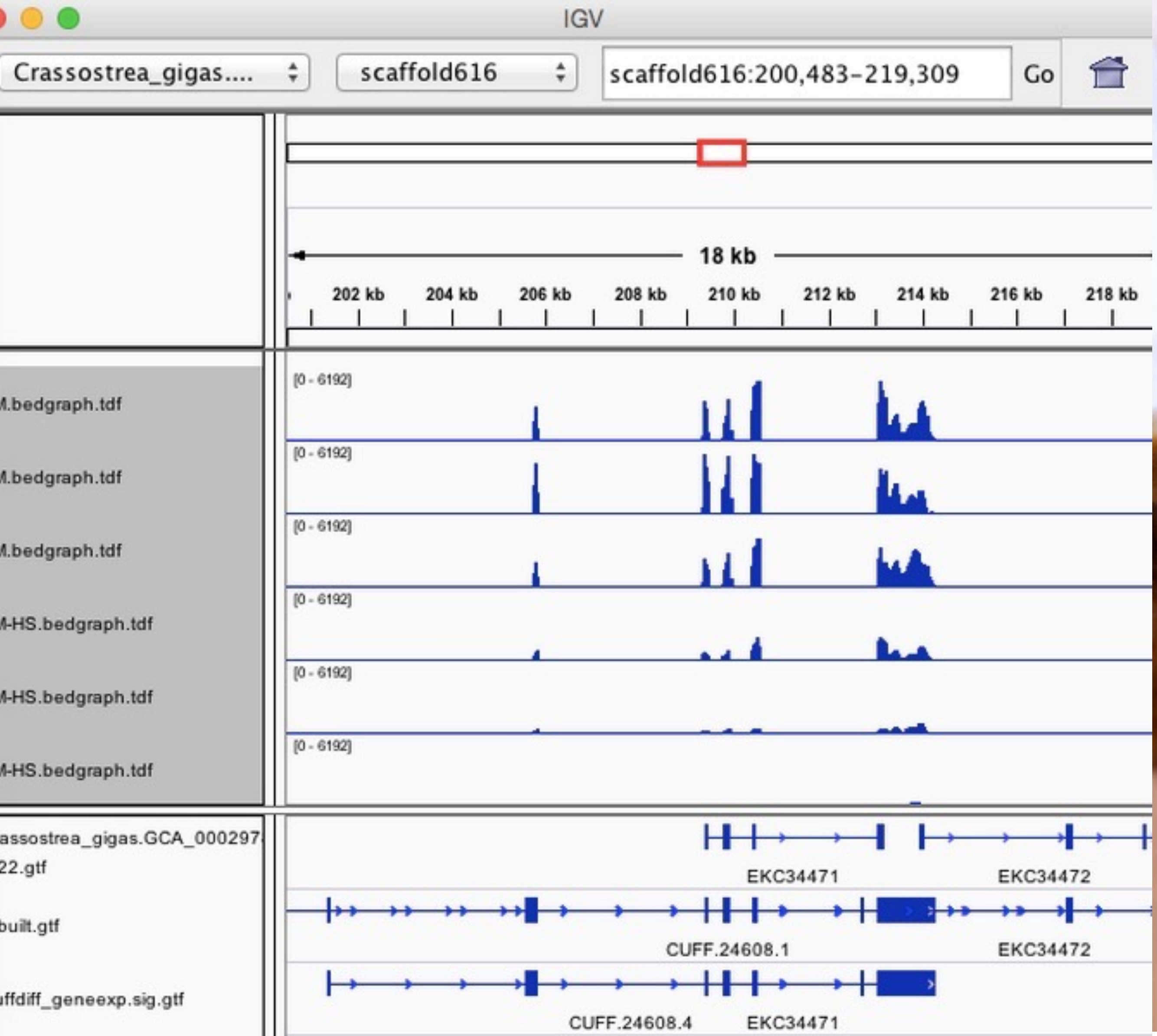
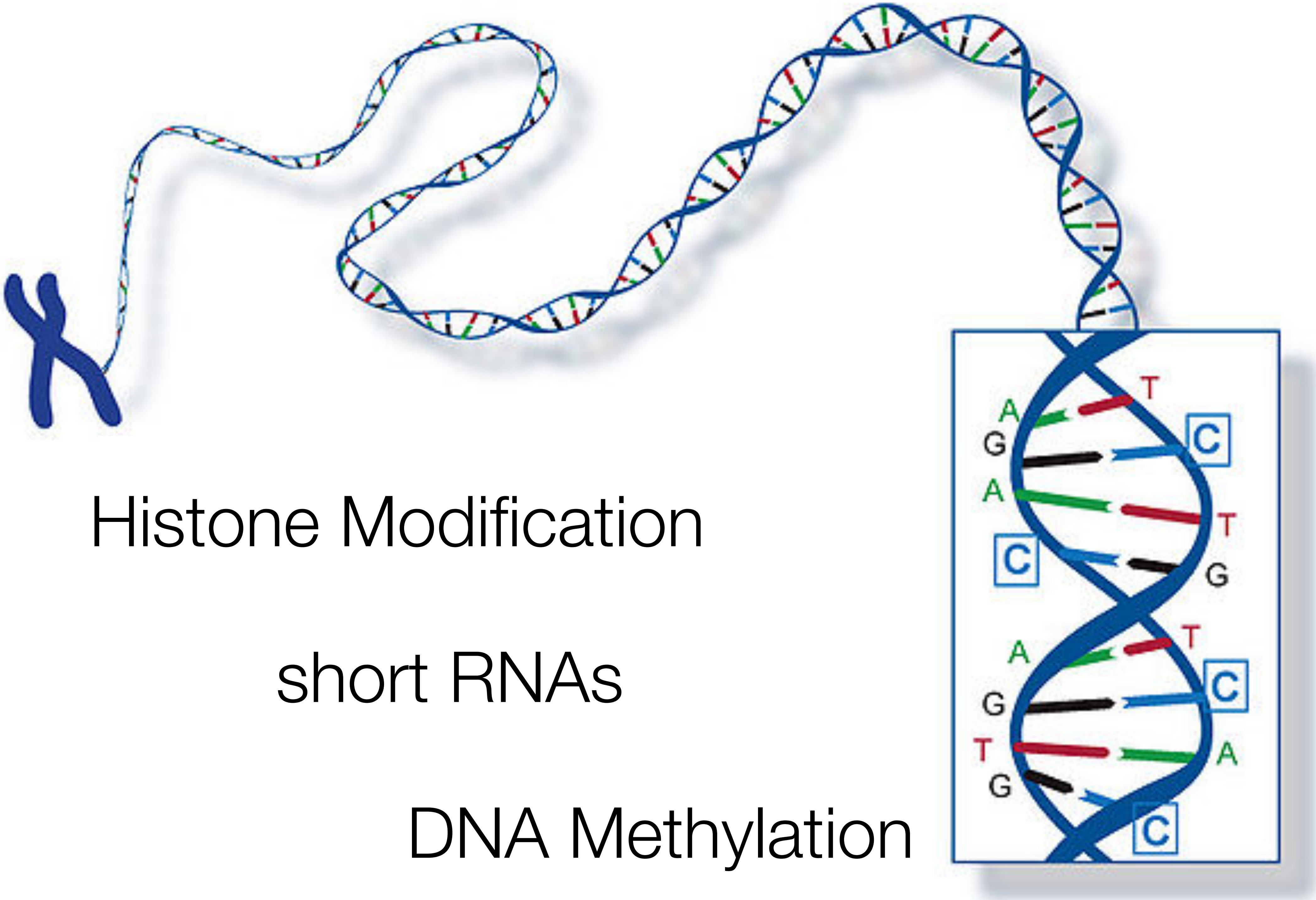
Genome Resources



Epigenetics



Histone Modification

short RNAs

DNA Methylation

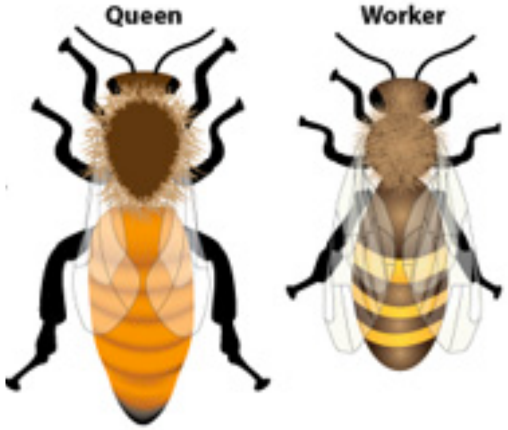
Epigenetics

Photo credit: Flickr, Creative Commons, he-boden

Epigenetics

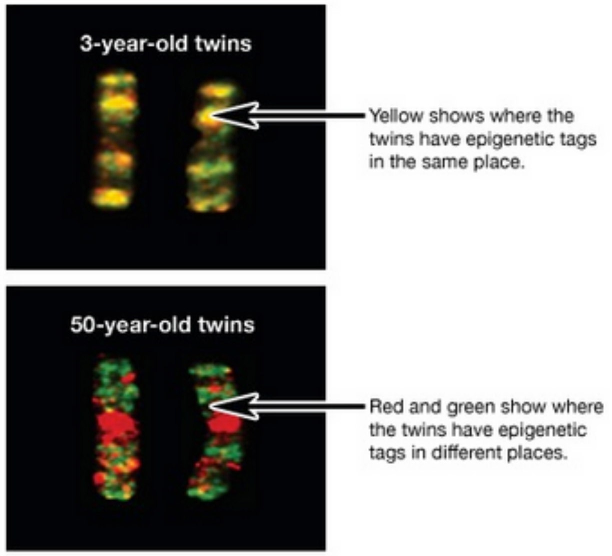
Learn.Genetics
GENETIC SCIENCE LEARNING CENTER

Queen Bee Larvae: Queens are raised in specially constructed cells called "queen cups," which are filled with royal jelly.



Nature AND Nurture

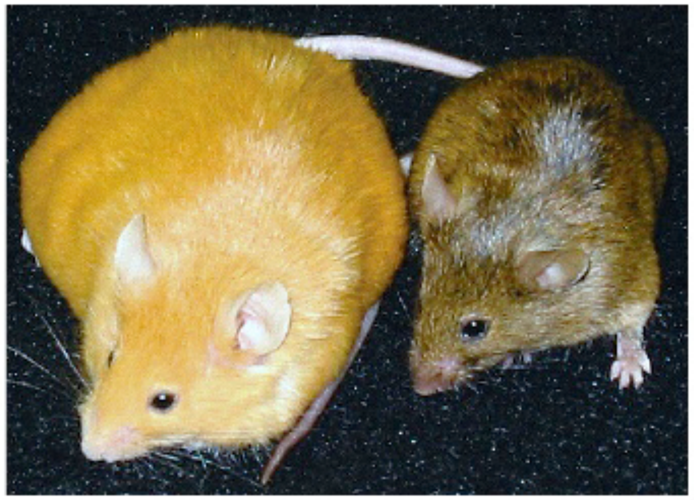
Chromosome 3 Pairs
3-year old twins vs. 50-year-old twins



Yellow shows where the twins have epigenetic tags in the same place.

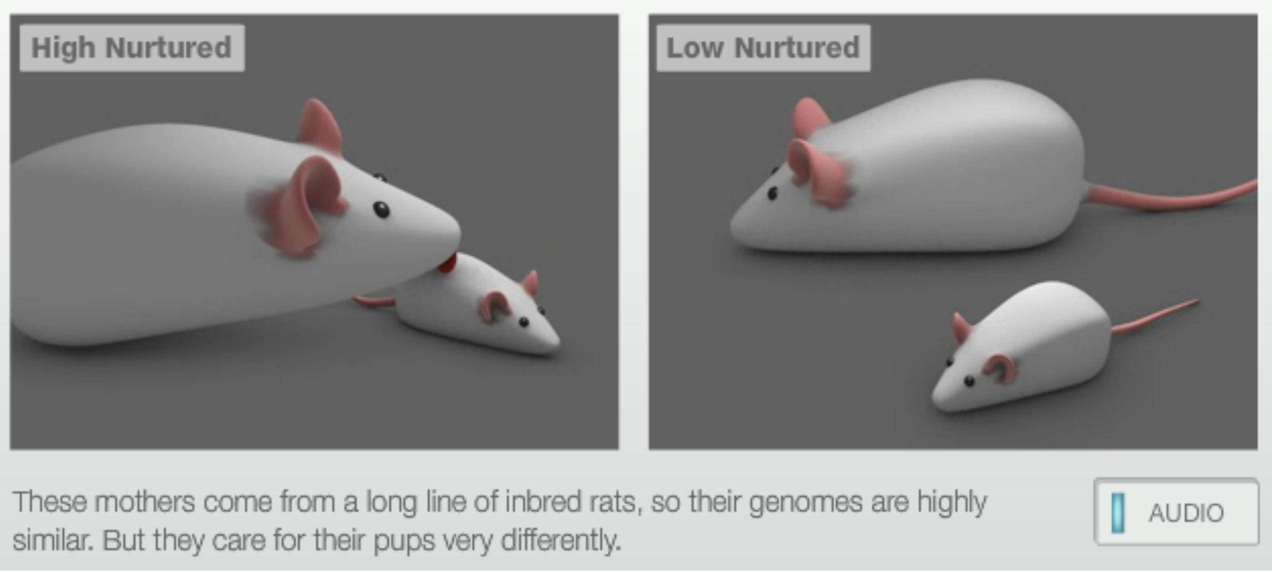
Red and green show where the twins have epigenetic tags in different places.

These Two Mice are Genetically Identical and the Same Age



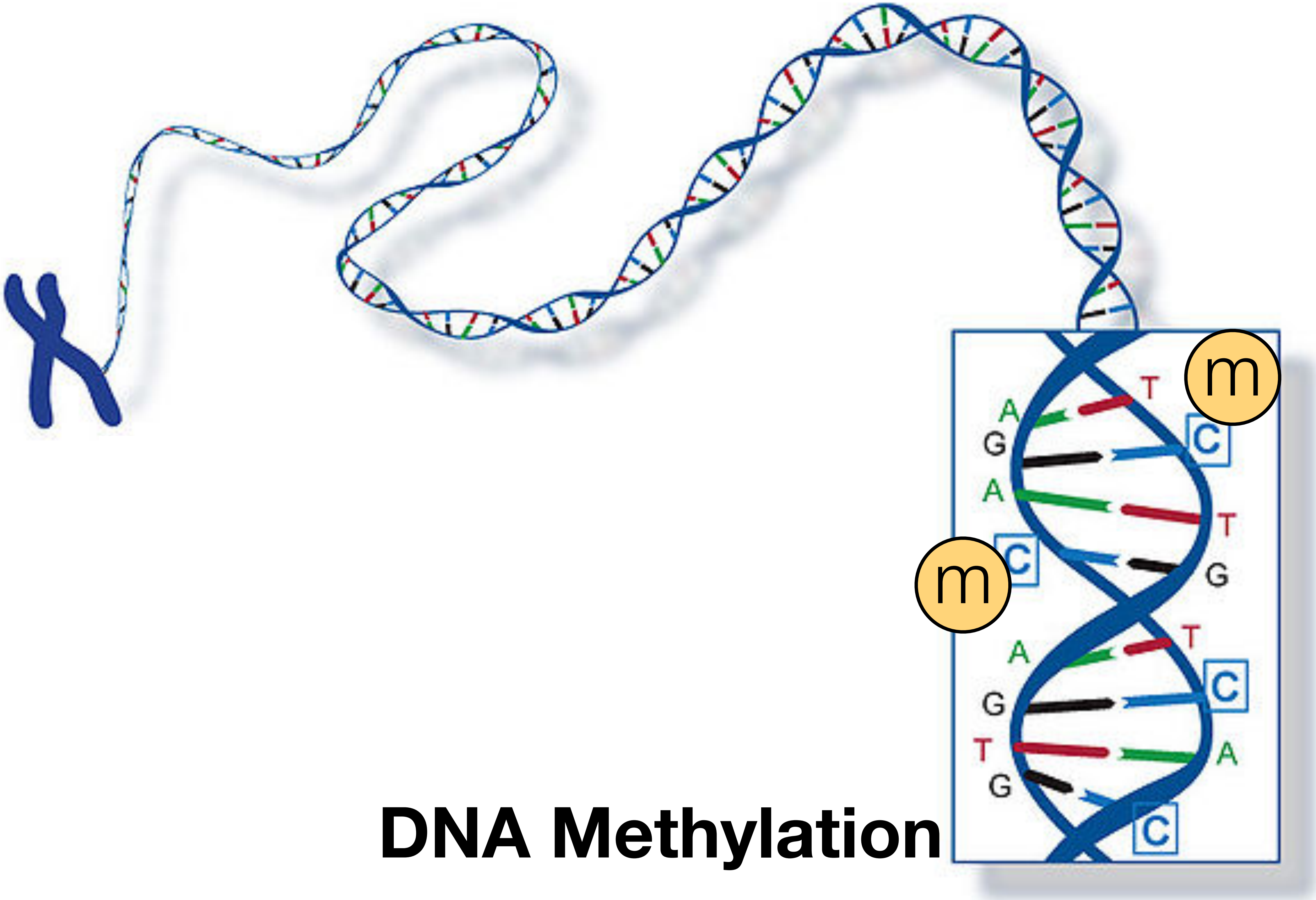
While pregnant, both of their mothers were fed Bisphenol A (BPA) but DIFFERENT DIETS:

The mother of this mouse received a **normal mouse diet**	The mother of this mouse received a diet **supplemented** with choline, folic acid, betaine and vitamin B12



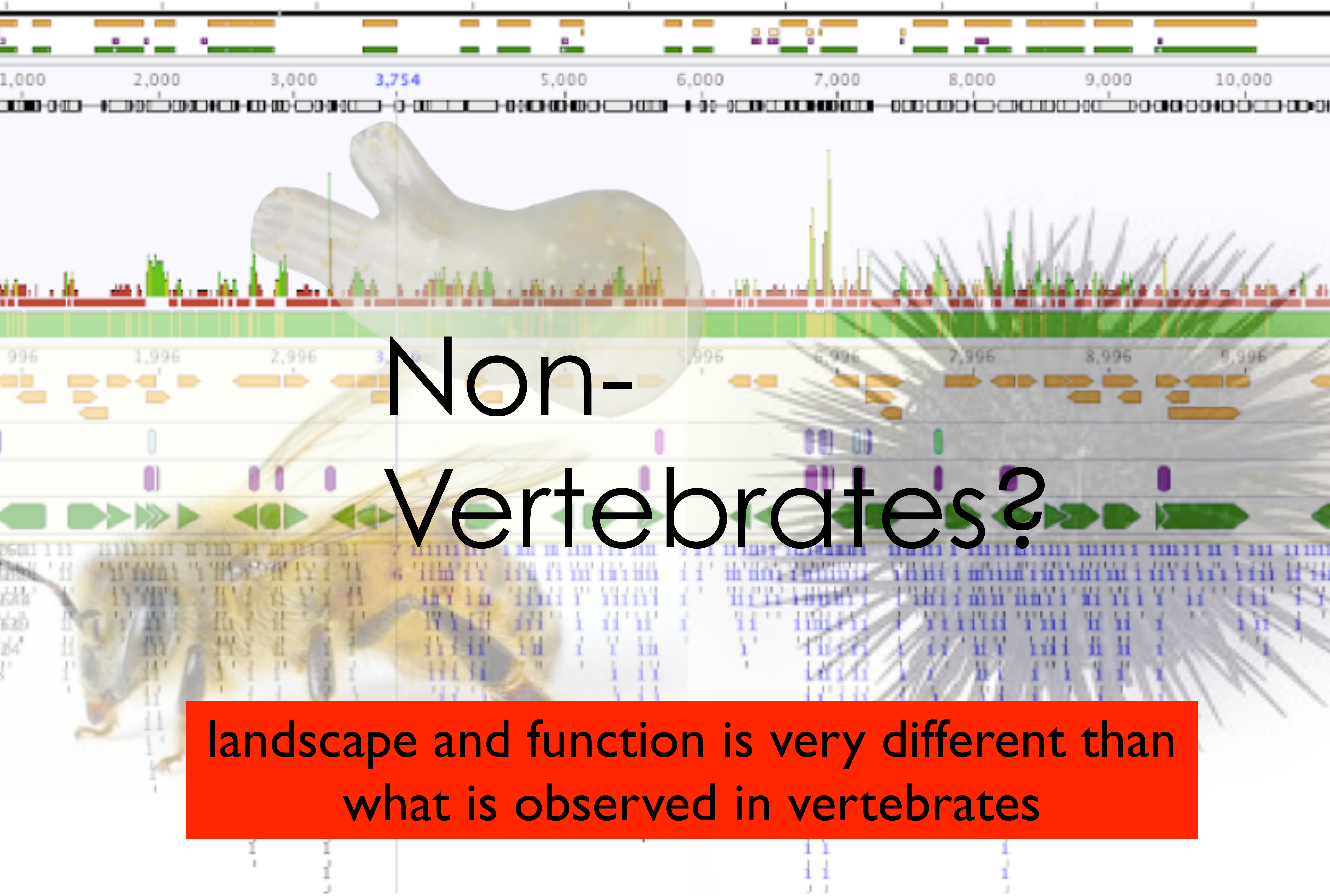
These mothers come from a long line of inbred rats, so their genomes are highly similar. But they care for their pups very differently.

http://learn.genetics.utah.edu

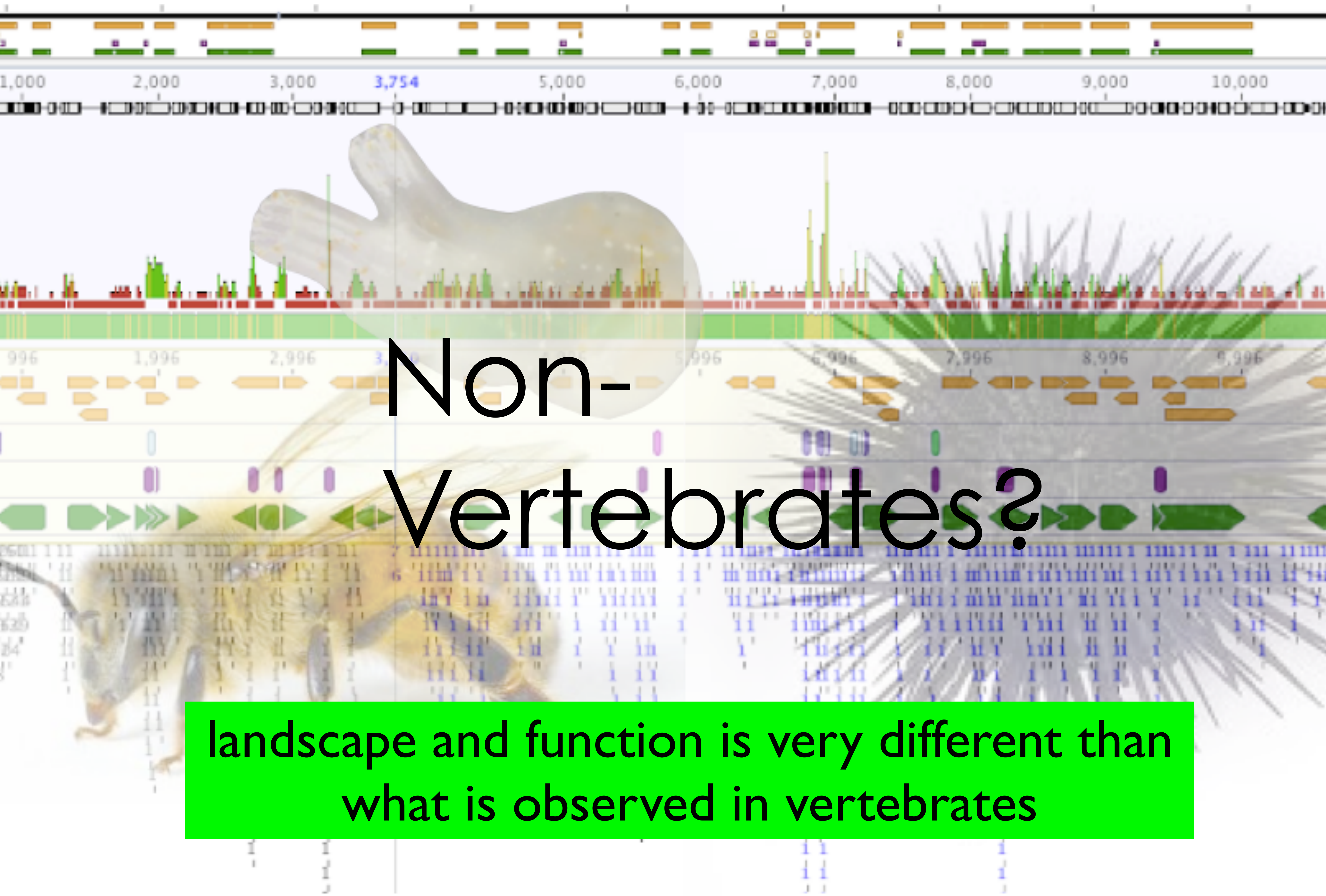


DNA Methylation

Non-Vertebrates?



landscape and function is very different than what is observed in vertebrates



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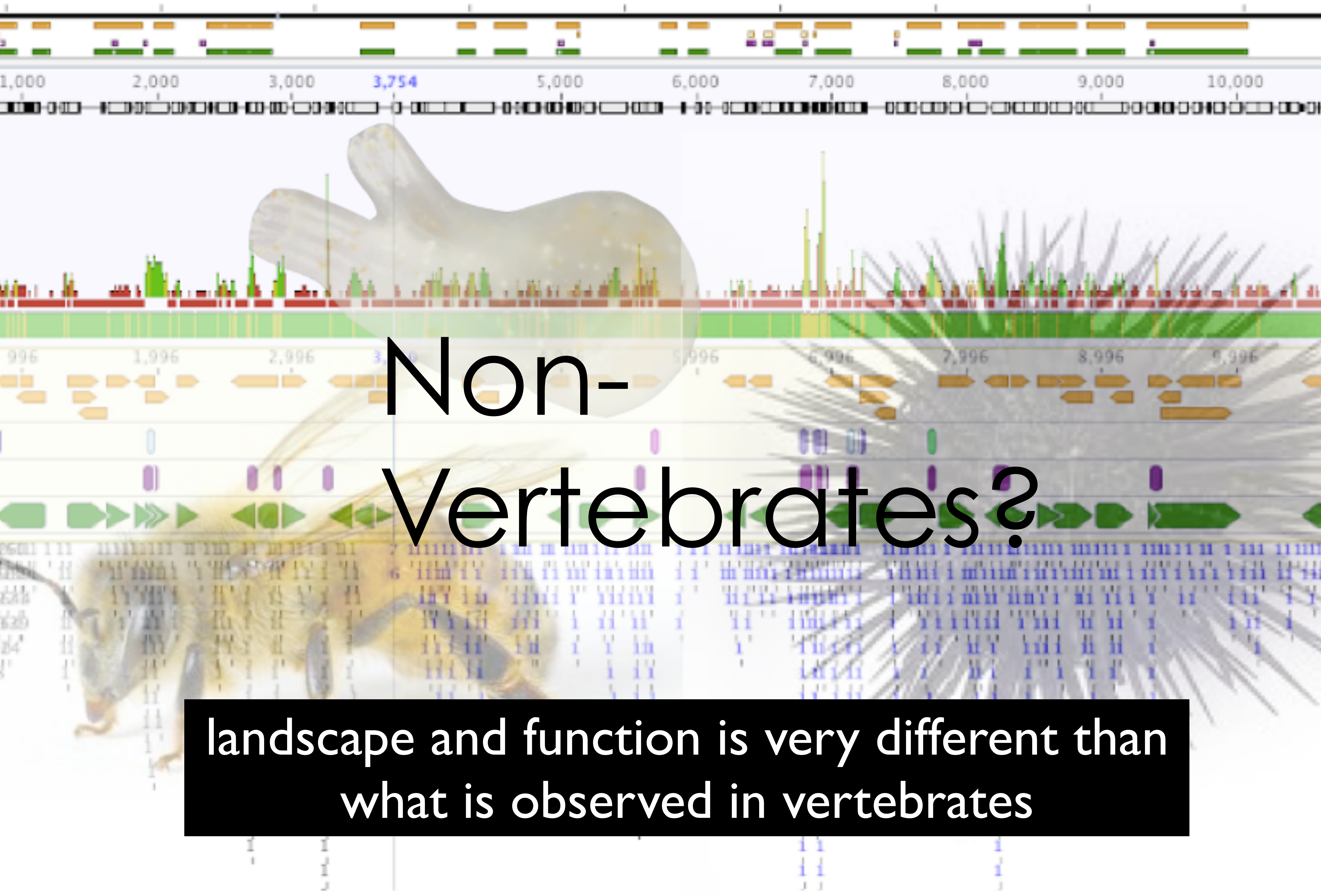


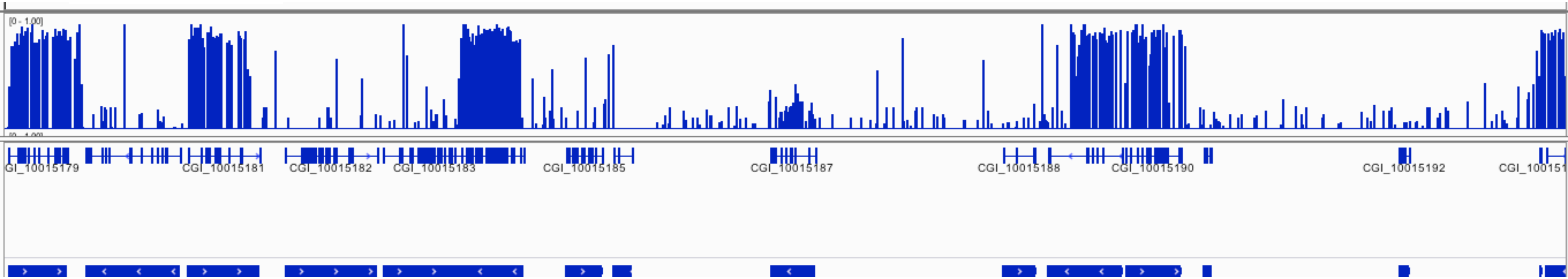
Non-Vertebrates?

landscape and function is very different than what is observed in vertebrates

Absent in
several
model
organisms

Oysters?

Epigenetic variation 1



mosaic

associated with gene bodies

Epigenetic variation **1**

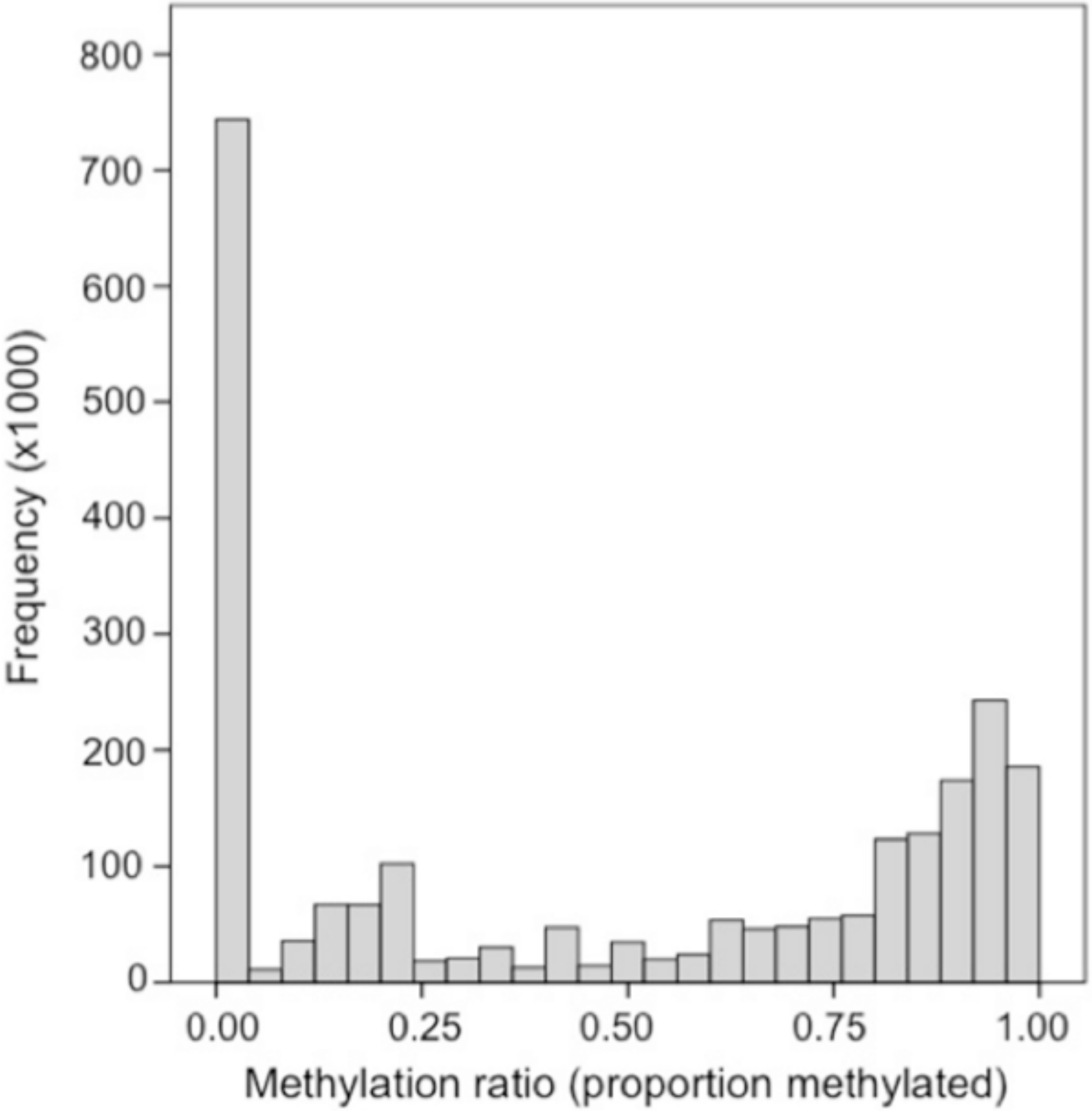
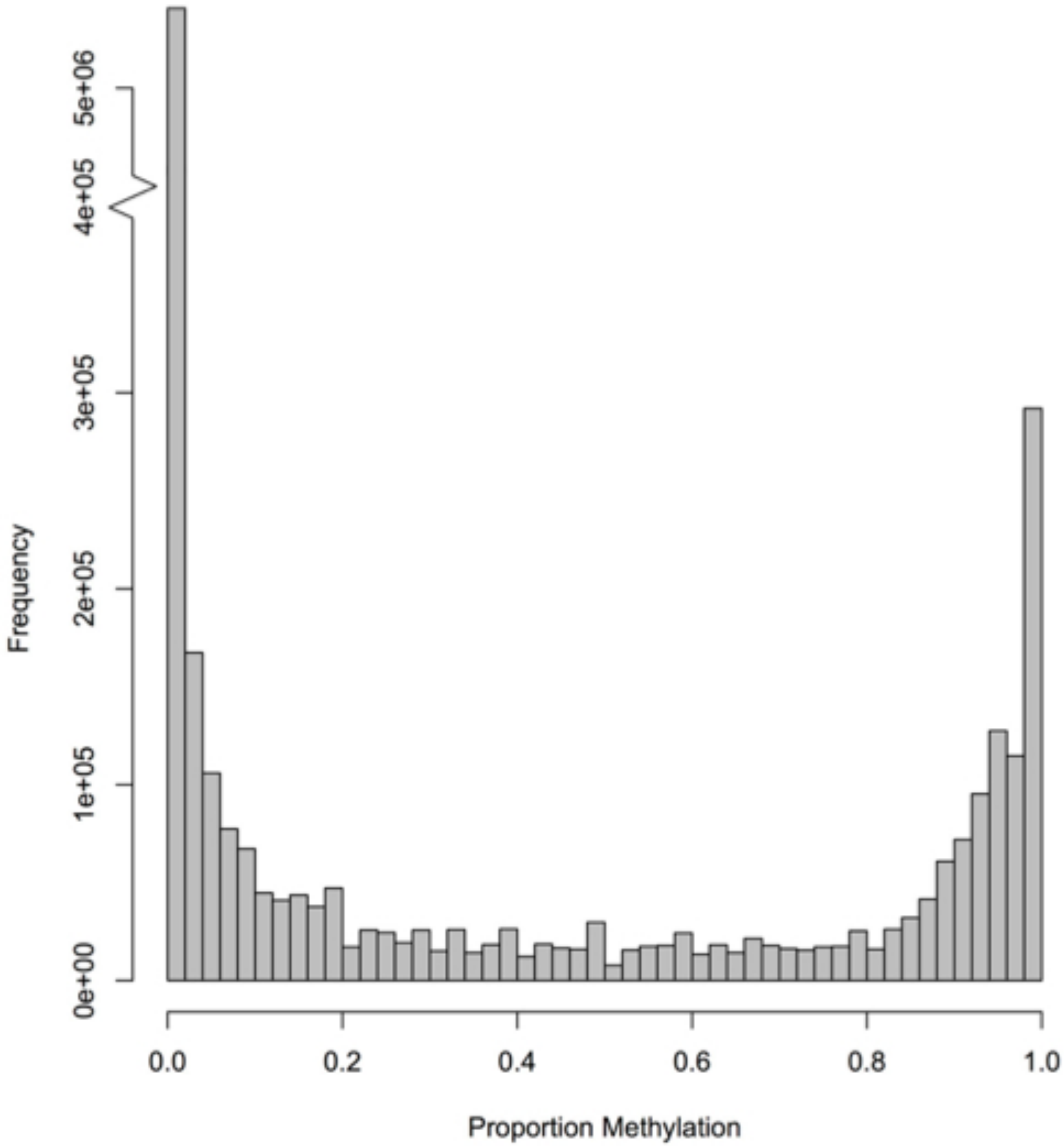


Figure 1 **Frequency distribution of methylation ratios for CpG dinucleotides in oyster gill tissue.** A total of 2,625,745 CpG dinucleotides with ≥5× coverage are represented.

Gavery and Roberts (2013), *PeerJ*, DOI 10.7717/peerj.215

Epigenetic variation 1

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ORIGINAL RESEARCH ARTICLE
published: 17 June 2014
doi: 10.3389/fphys.2014.00224

Genome-wide profiling of DNA methylation and gene expression in *Crassostrea gigas* male gametes

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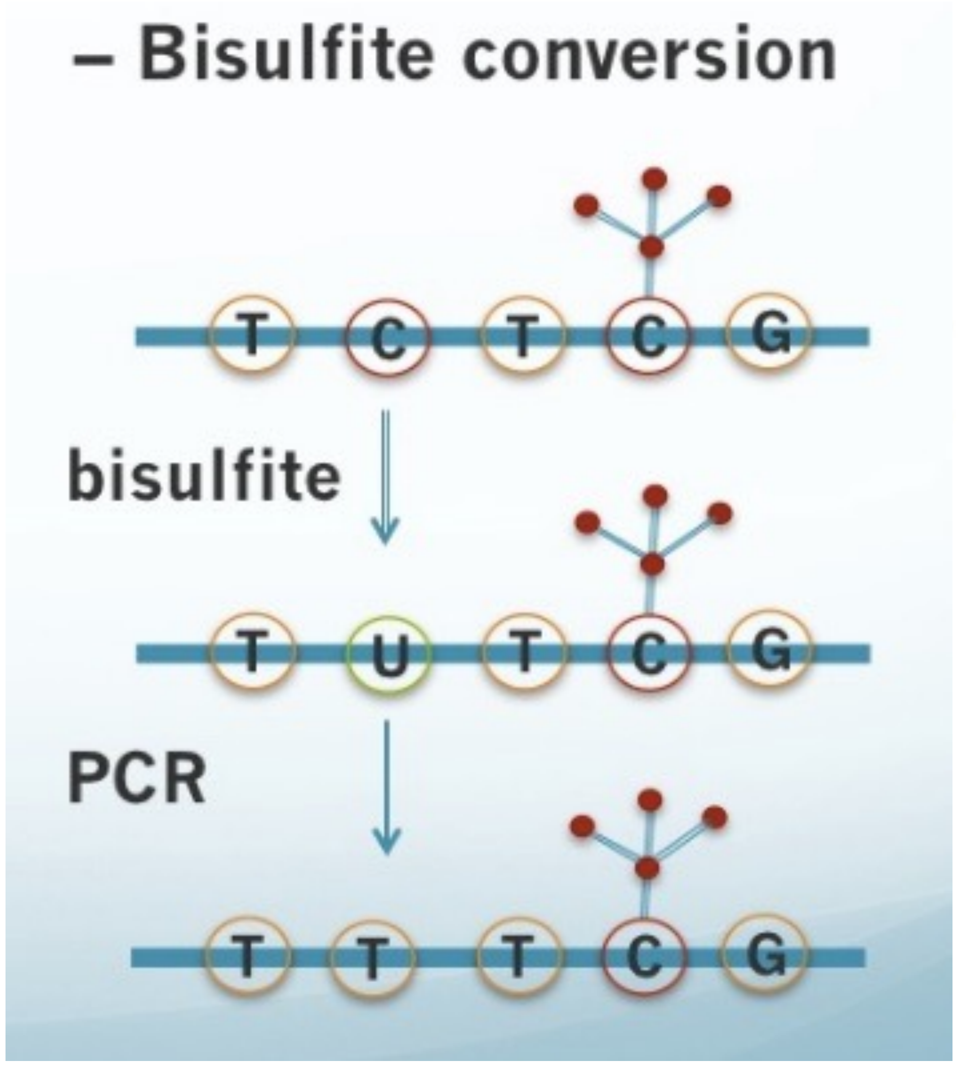

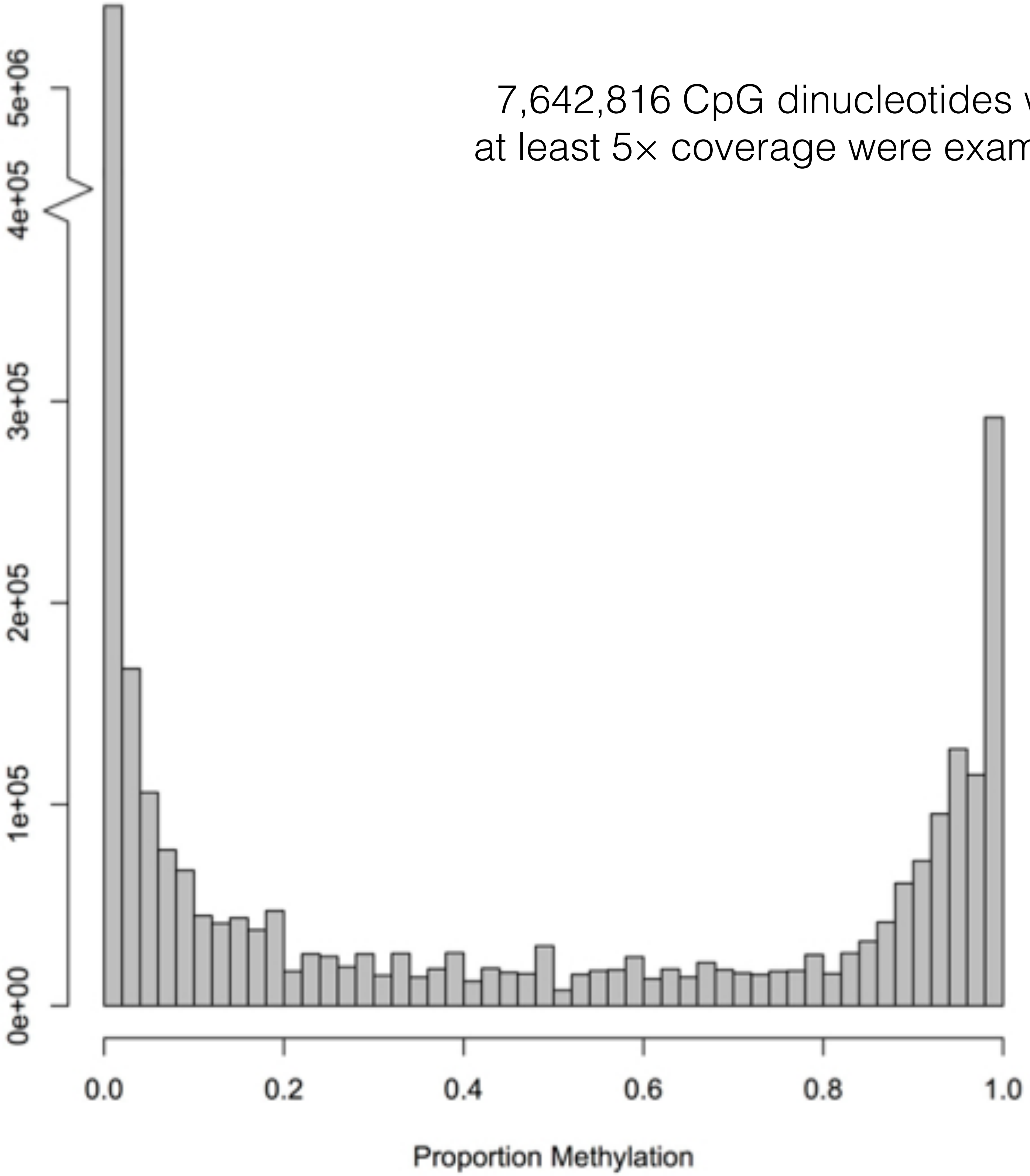

7,642,816 CpG dinucleotides with
at least 5× coverage were examined


frontiers in
PHYSIOLOGY

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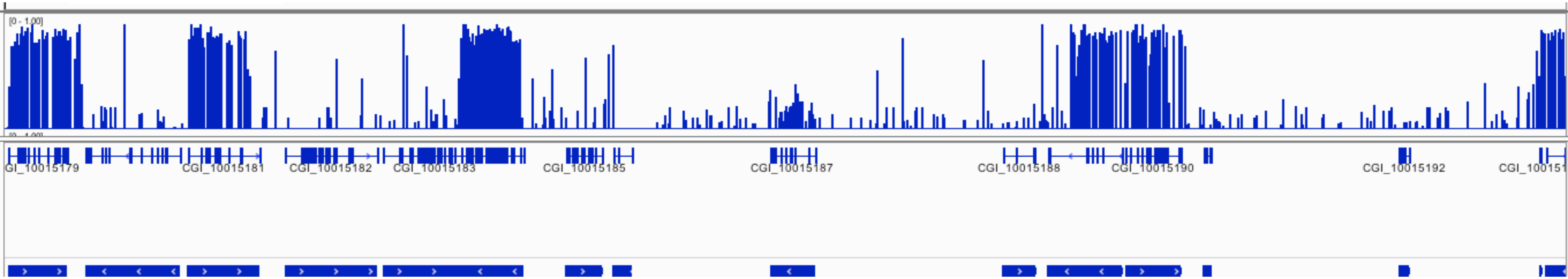

mosaic

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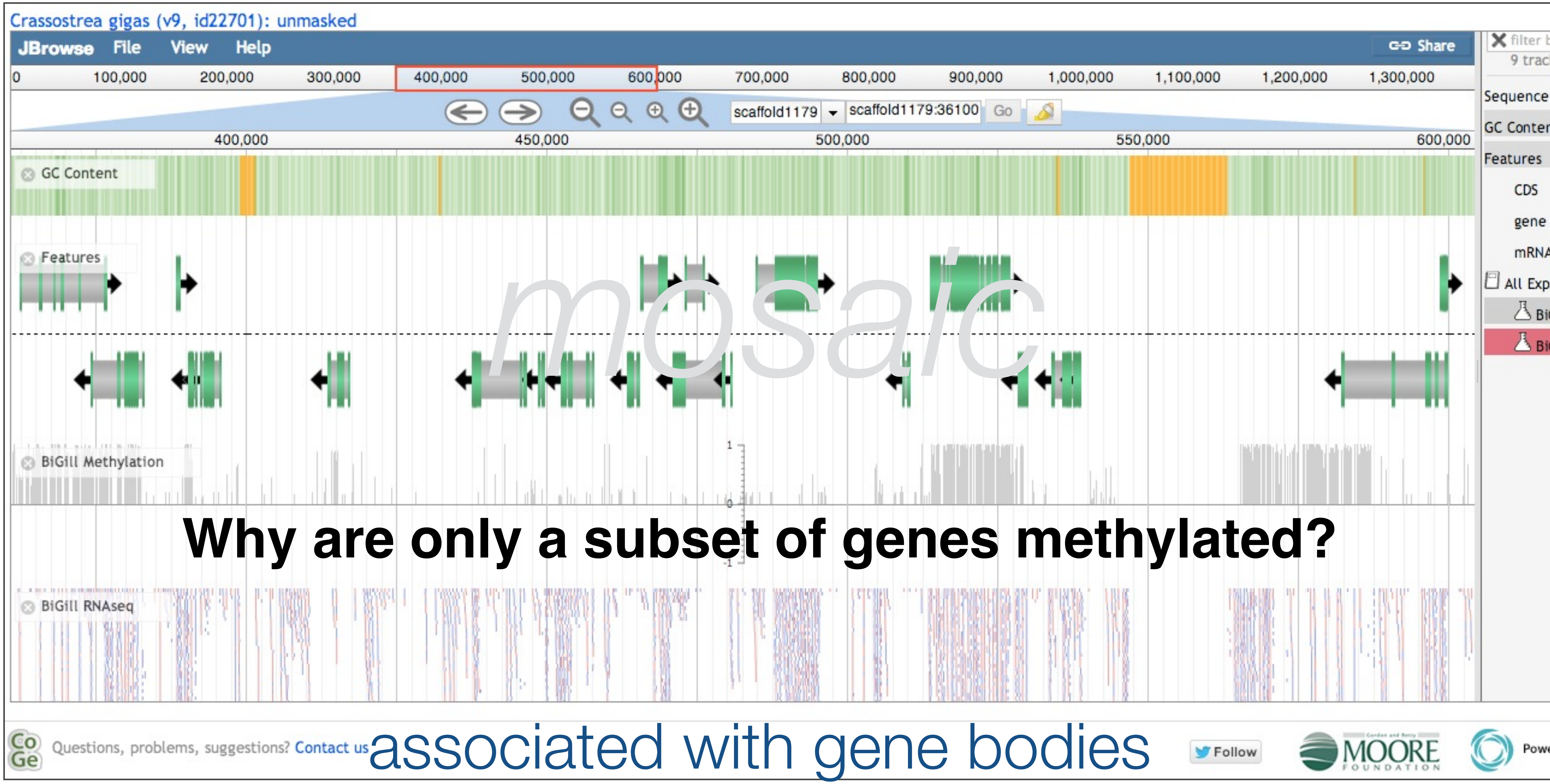
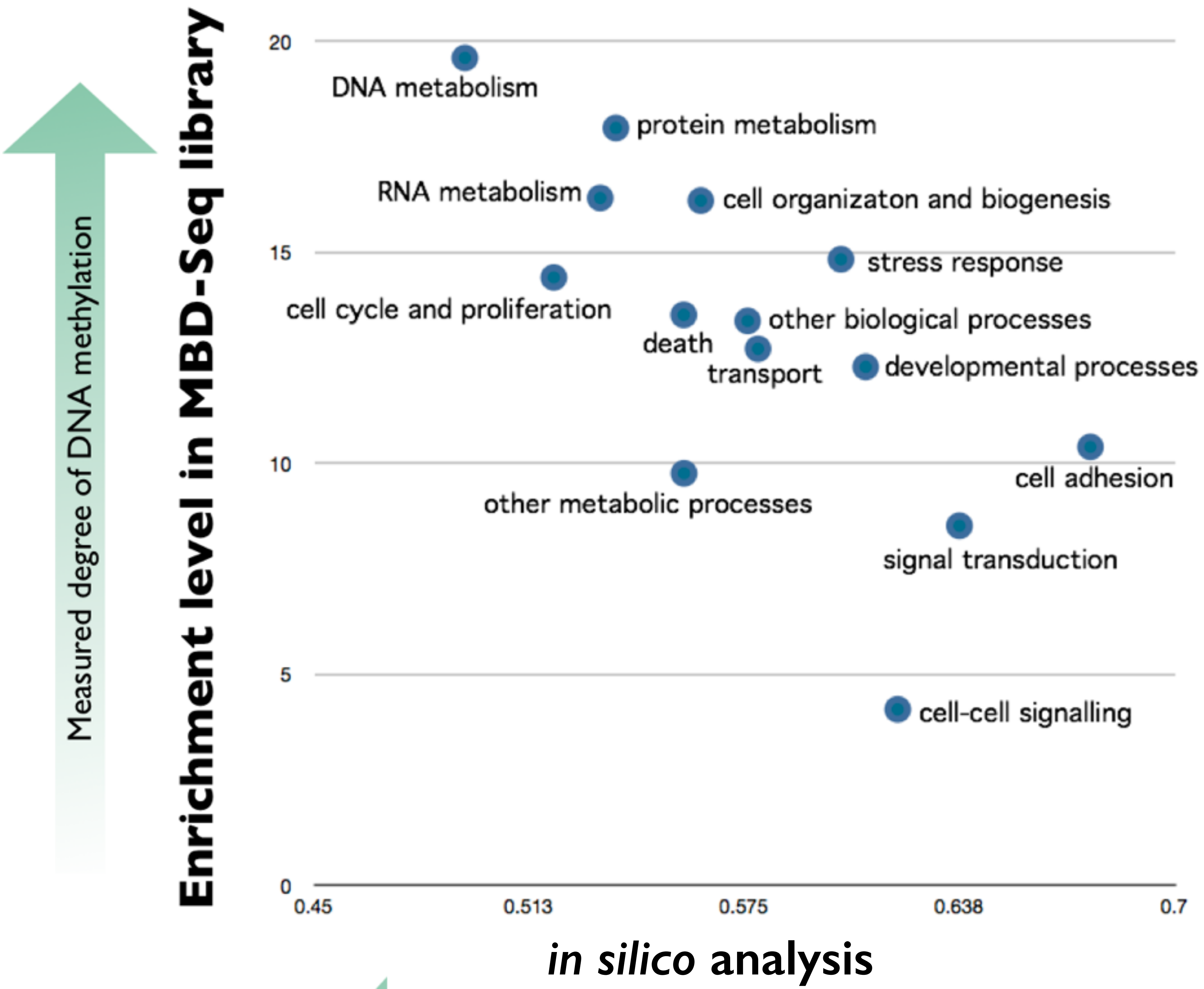


mosaic

Why are only a subset of genes methylated?

associated with gene bodies

Epigenetic variation 1

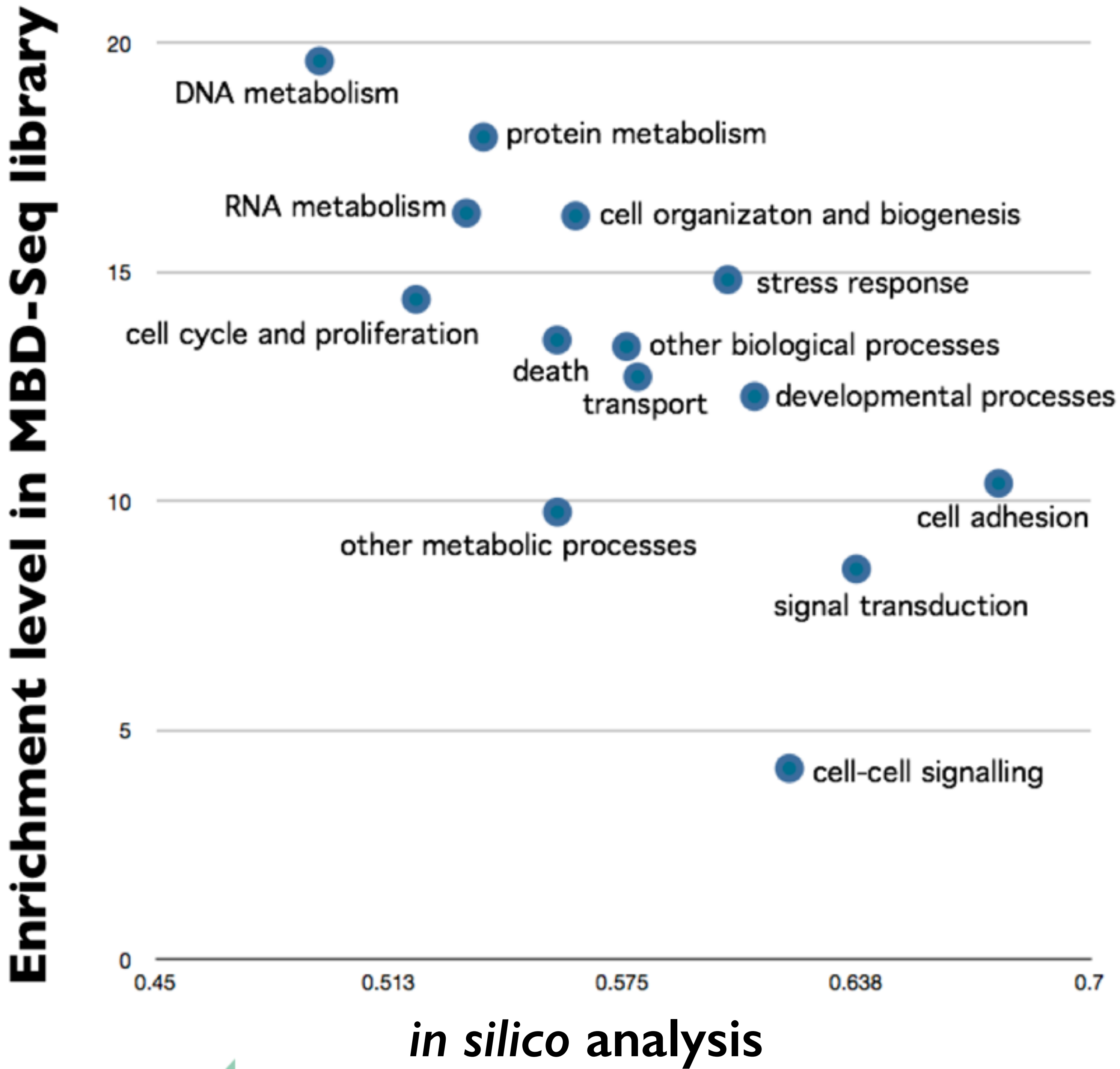


(modified from Gavery and Roberts 2010)

Predicted degree of DNA methylation

Roberts and Gavery 2012

Epigenetic variation **1**



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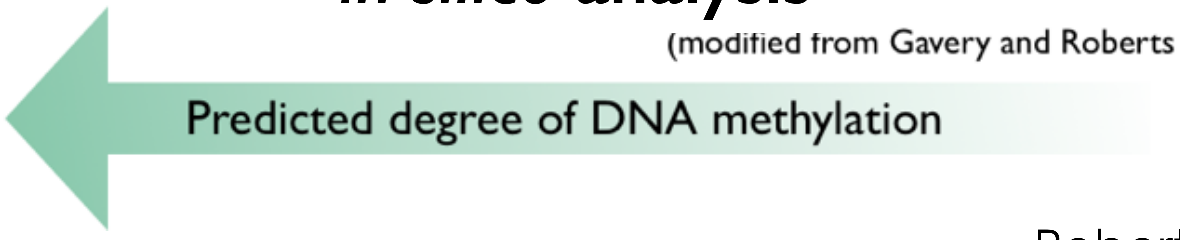


Roberts and Gavery 2012

in silico approach

- Principle:
  - Methylated cytosines are highly mutable

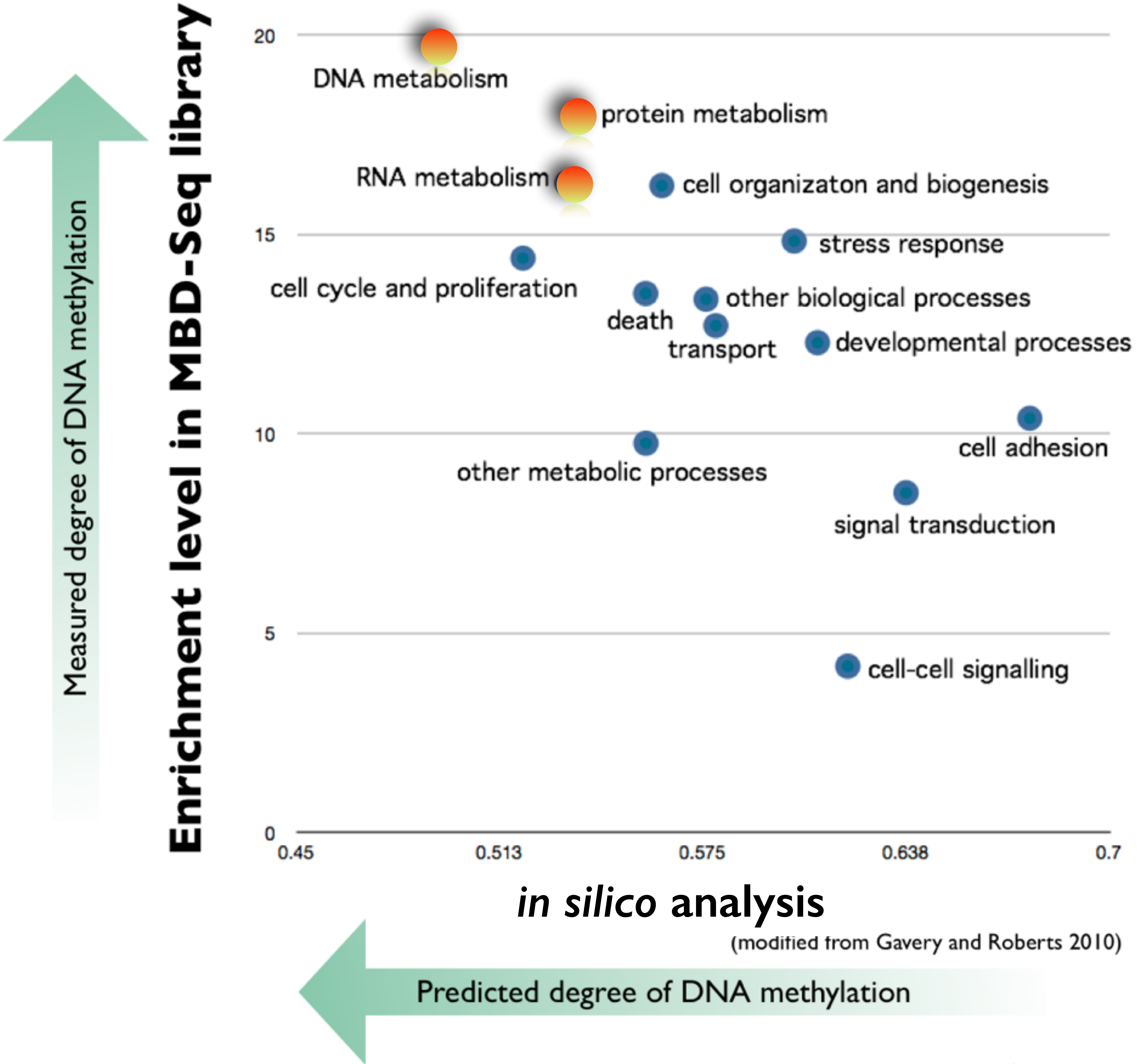
$$\overset{m}{\overset{|}{C}} \rightarrow T$$

  - Methylated regions of DNA are depleted of CpG dinucleotides over evolutionary time (CpG to TpG)

$$\text{CpG O/E} = \frac{\text{CpG observed}}{\text{CpG expected}}$$

↑ high = unmethylated

Epigenetic variation 1



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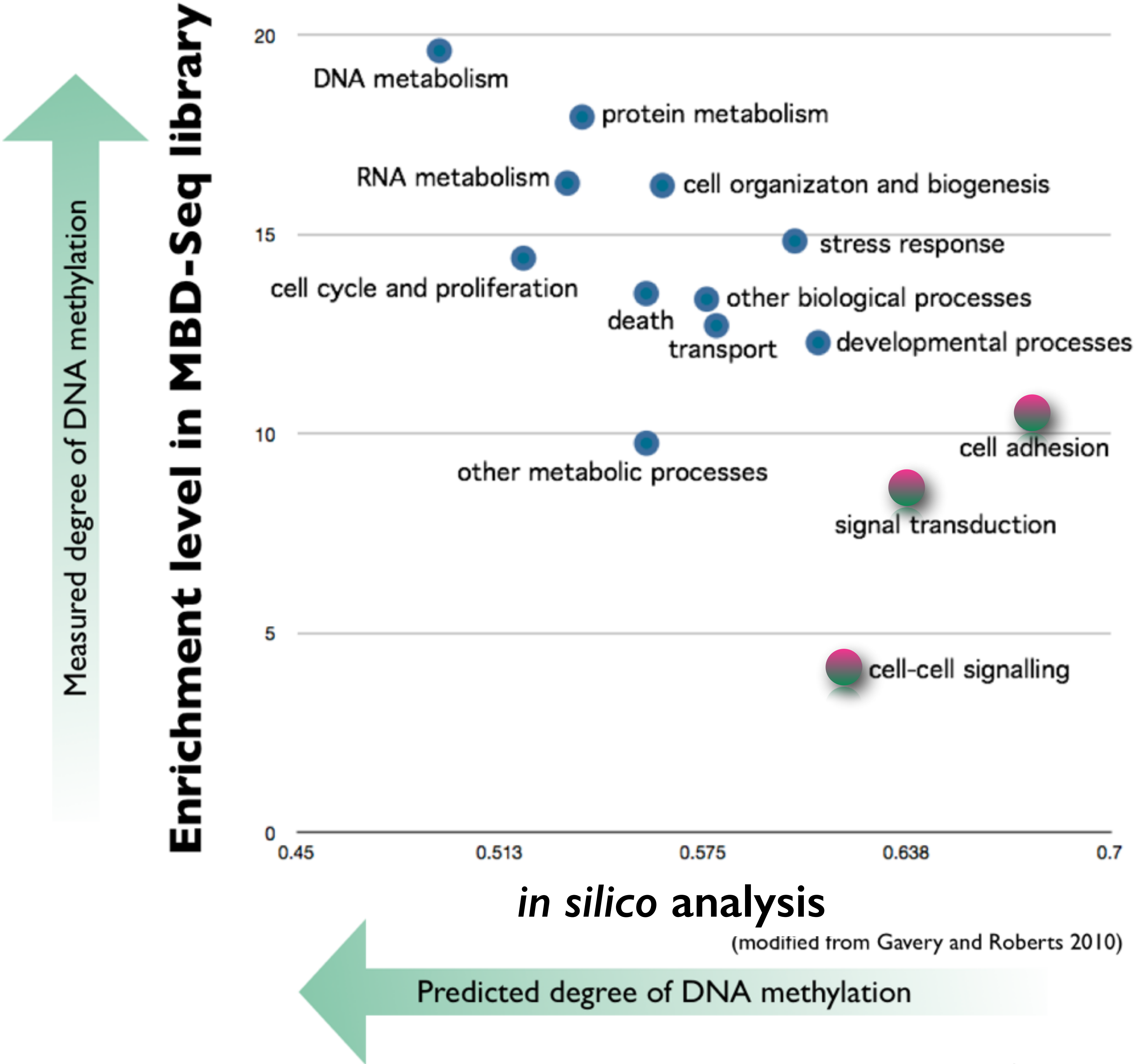

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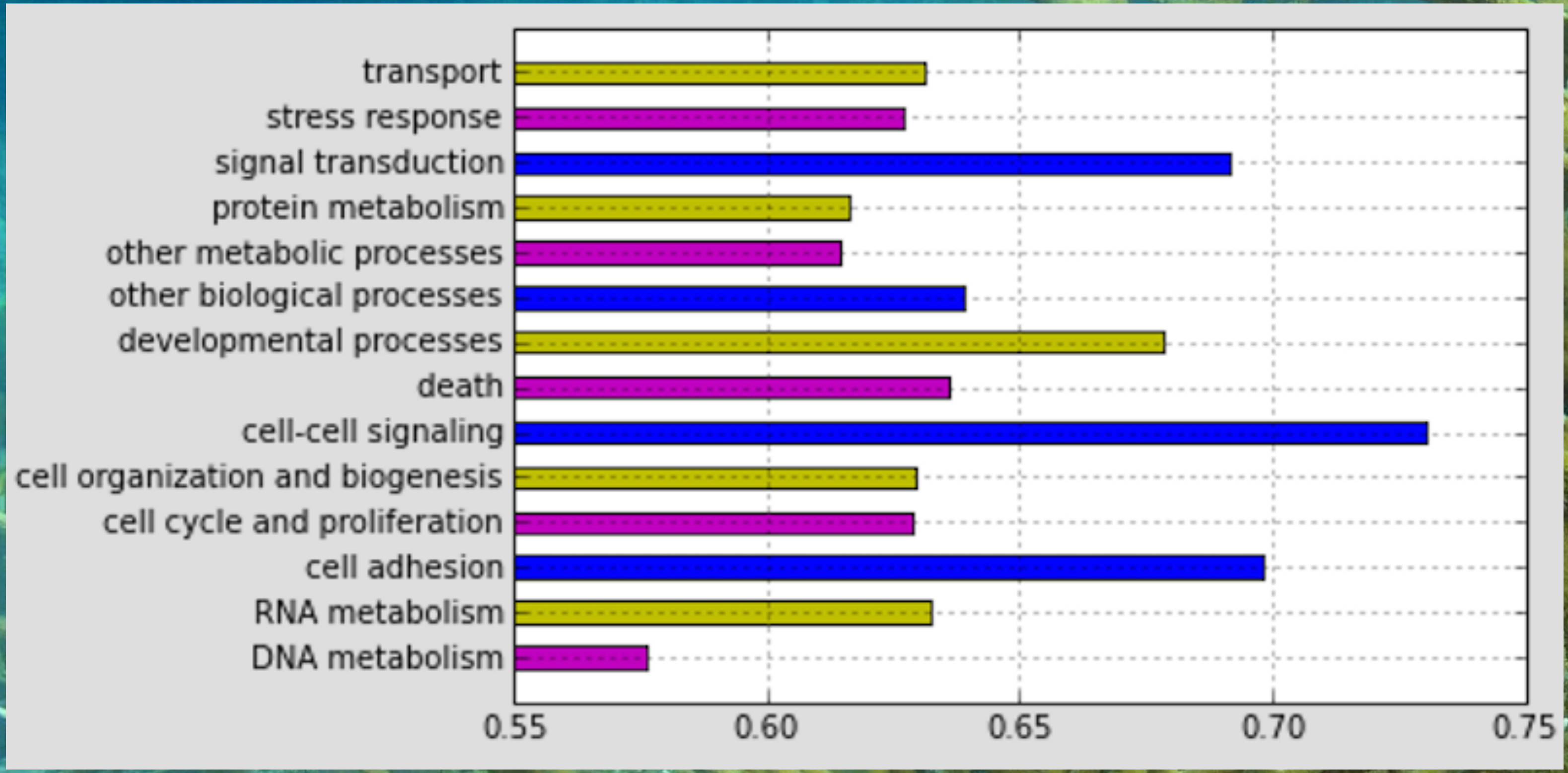
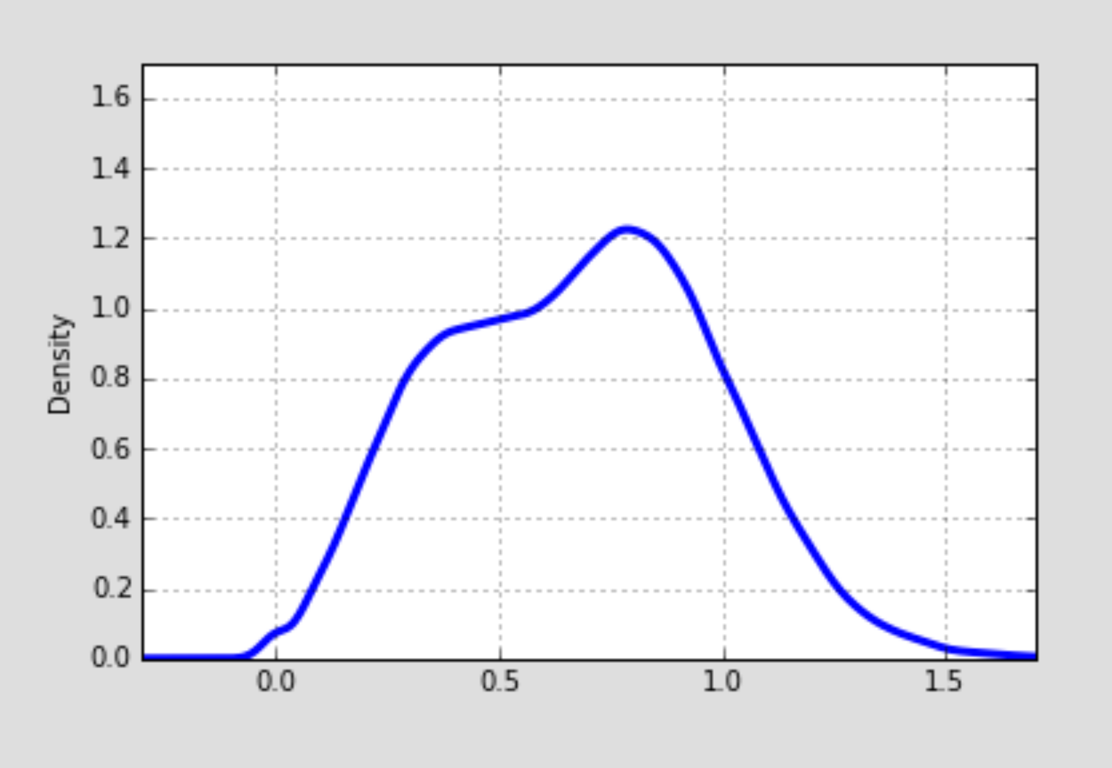
Roberts and Gavery 2012


Jay Dimond
Acropora palmata
Acropora cervicornis

Jay Dimond

Acropora palmata





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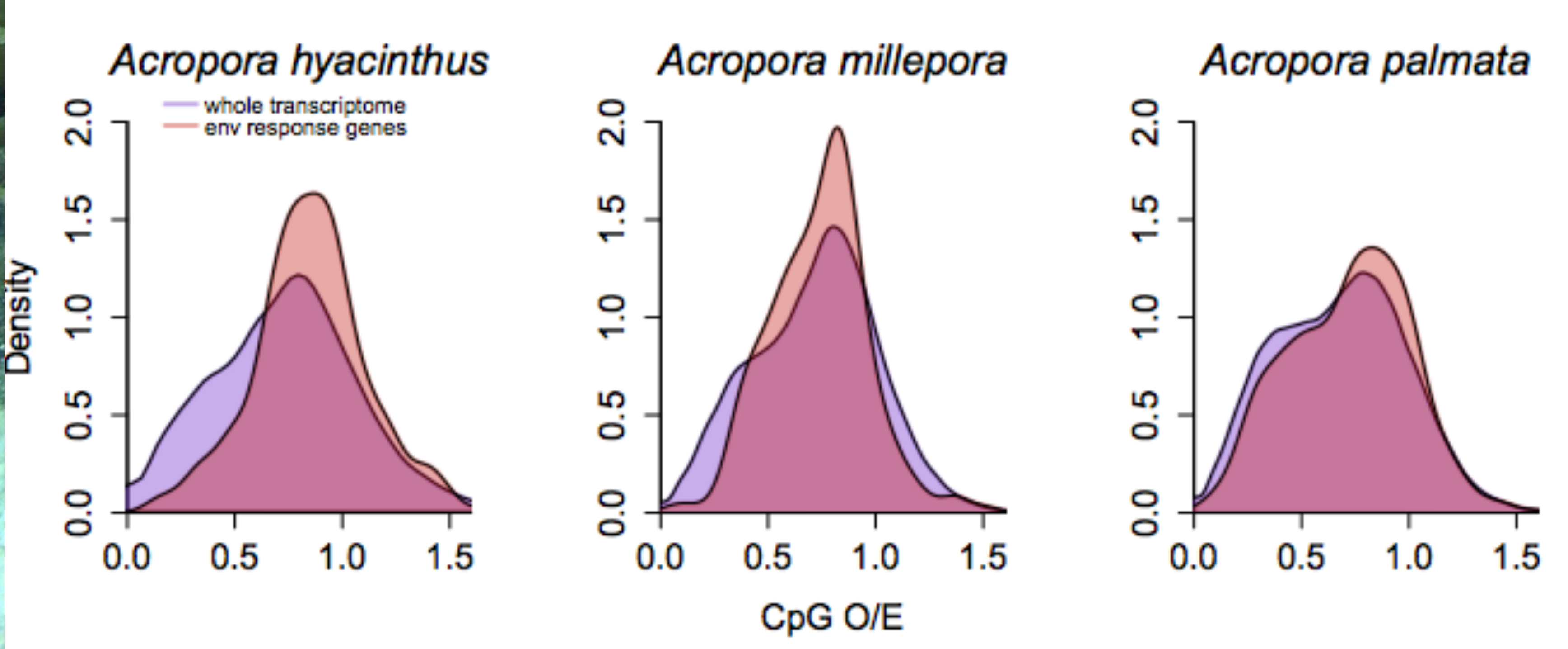
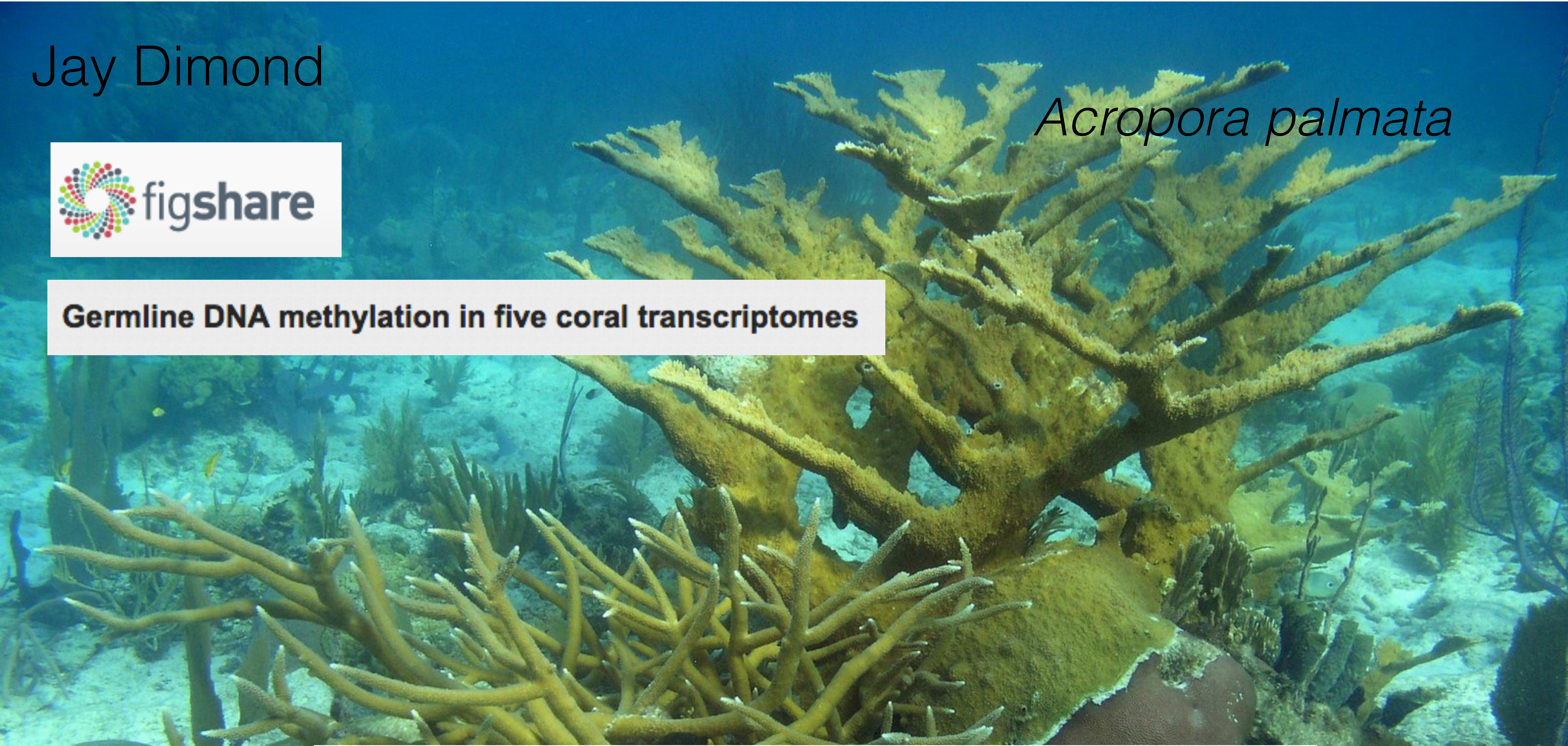
Acropora palmata



Jay Dimond

figshare

Germline DNA methylation in five coral transcriptomes



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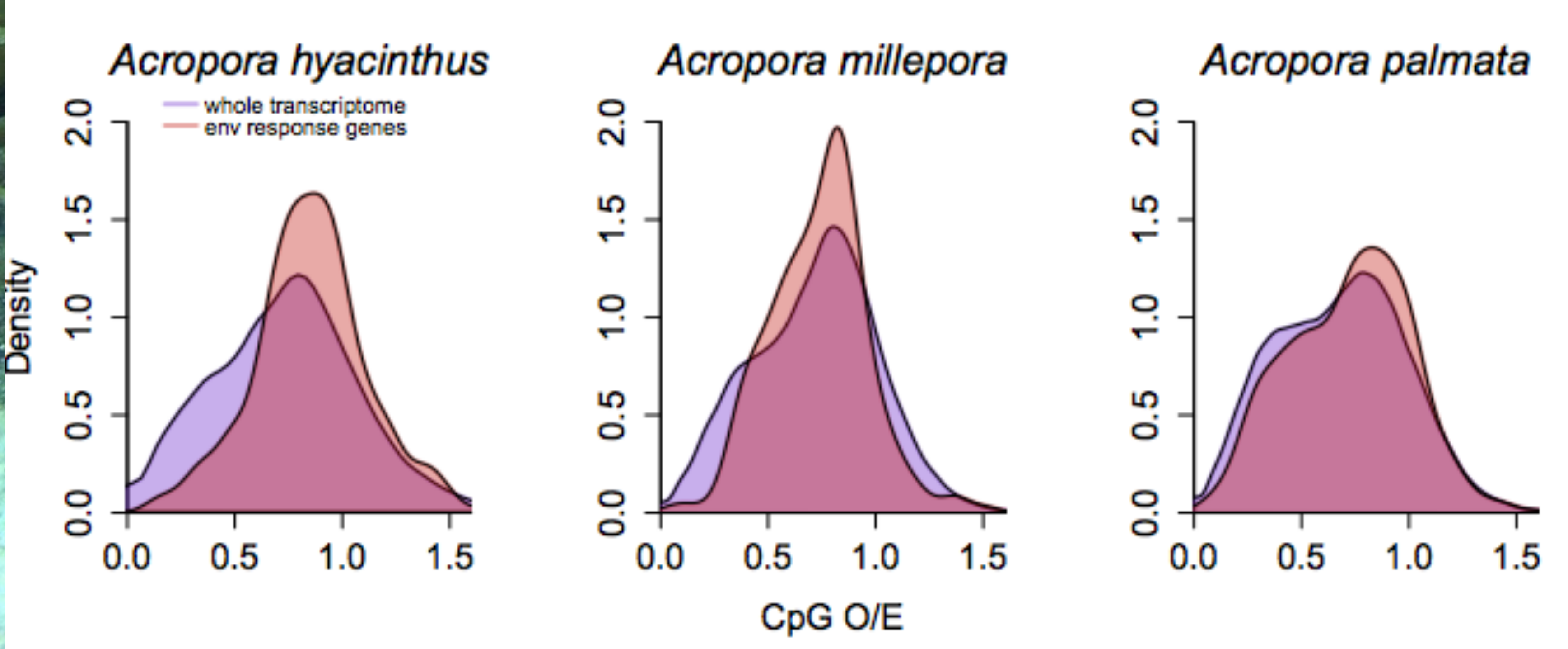

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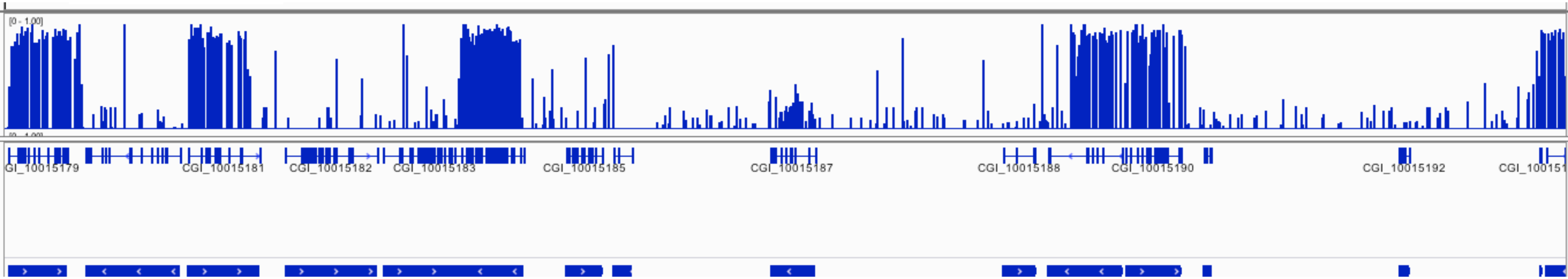


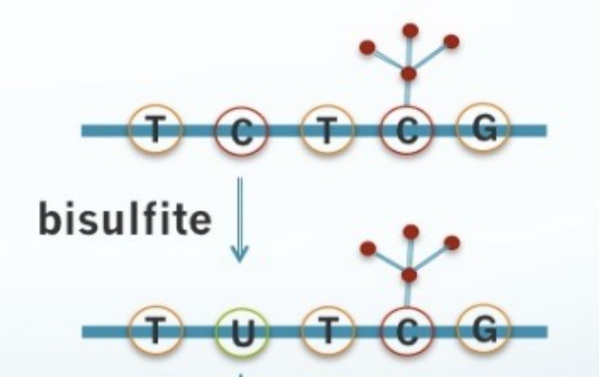
mosaic

associated with gene bodies
based on gene function

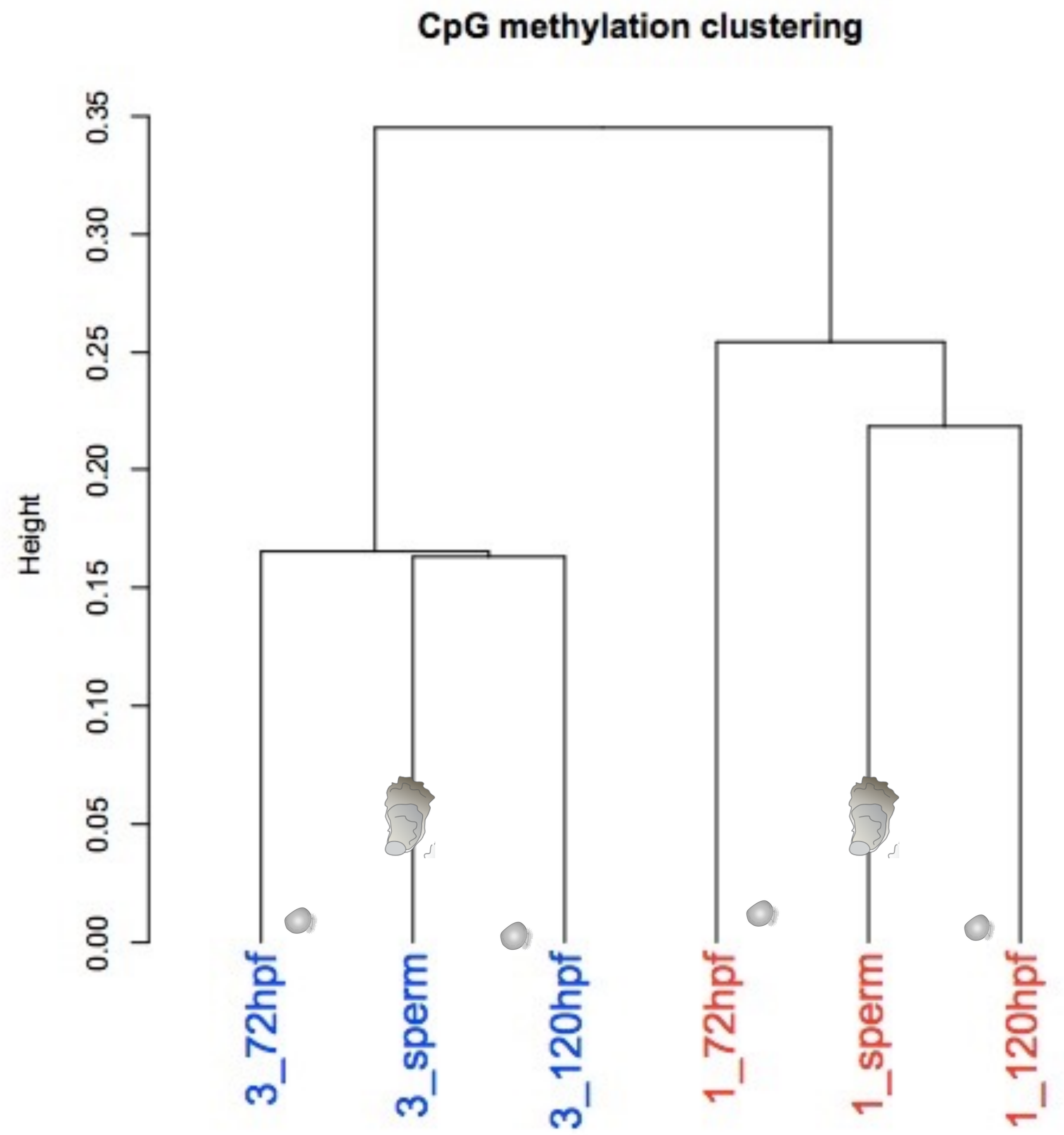
explanation?

Epigenetic variation **1**

Family and Developmental Variation



Sperm &
Larvae
(72h & 120h)


CpG methylation clustering

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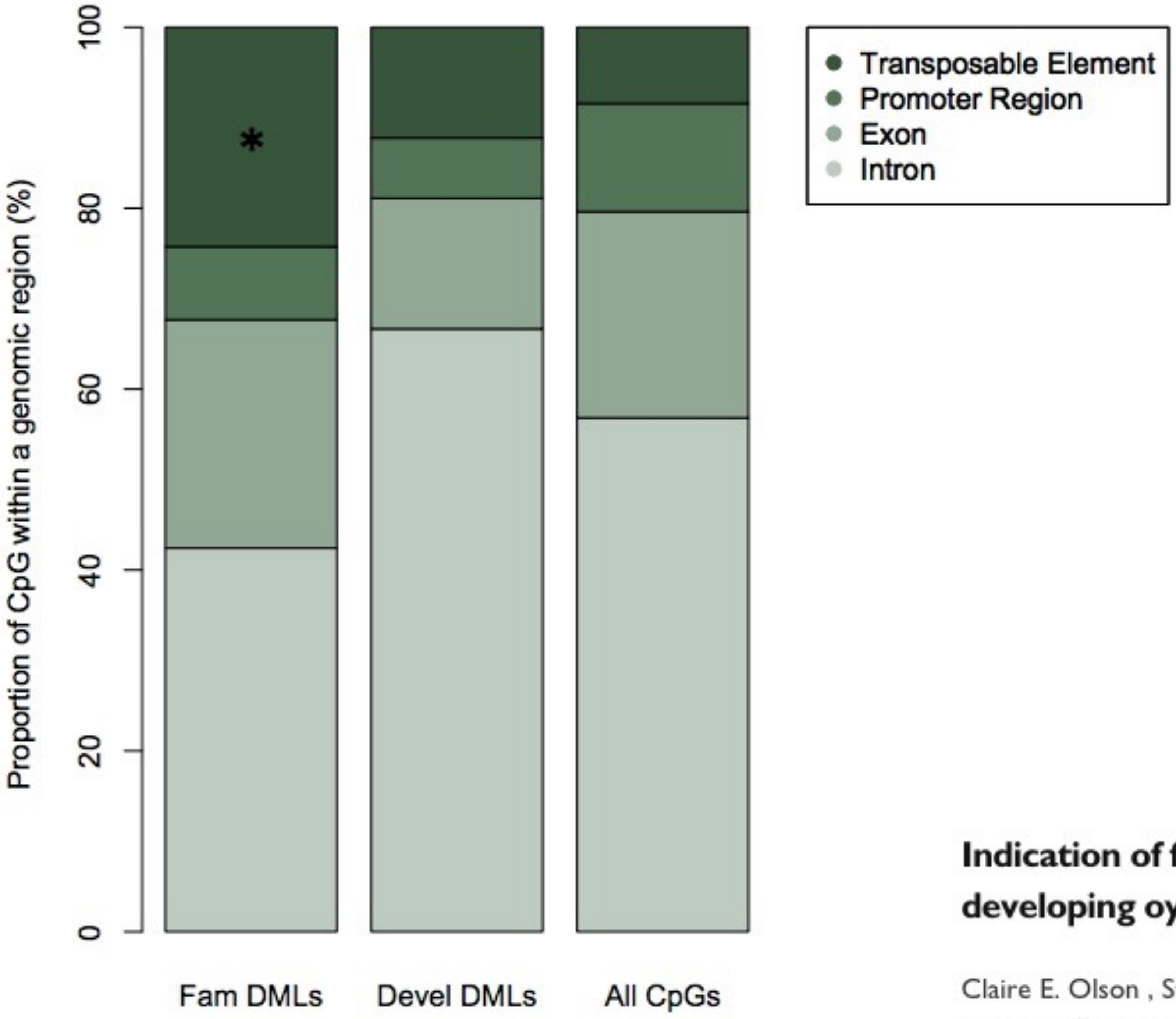
New Results

Indication of family-specific DNA methylation patterns in developing oysters

Claire E. Olson , Steven B. Roberts

doi: http://dx.doi.org/10.1101/012831

Epigenetic variation 1



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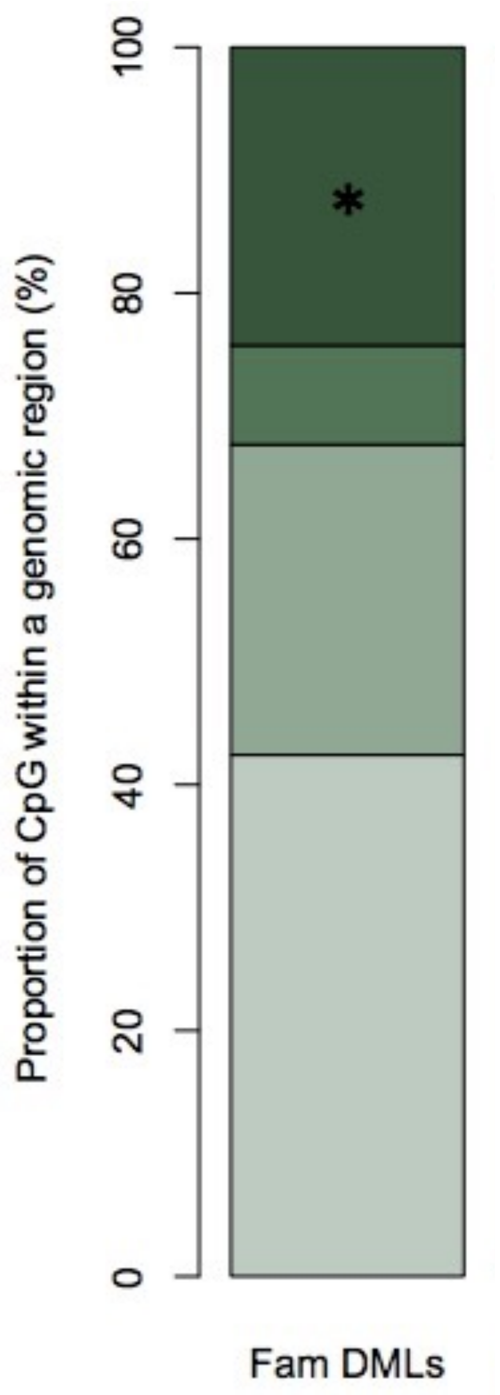
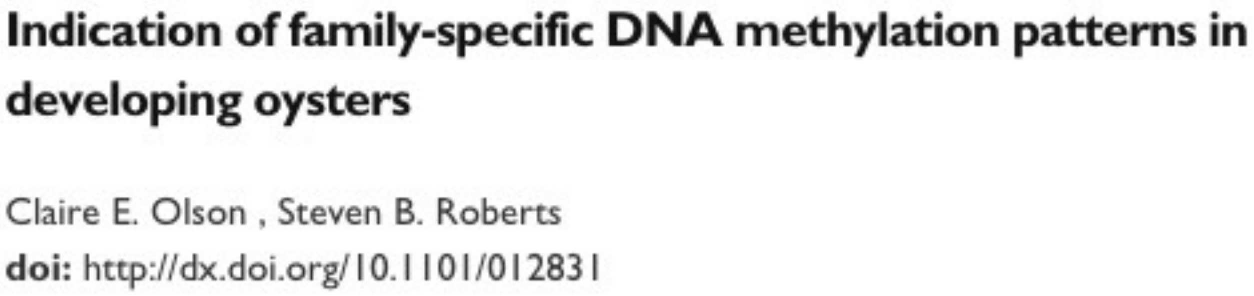


Differentially methylated loci in gene bodies could be lethal or deleterious, as they would alter gene expression.

Another possibility is that differentially methylated loci may provide advantageous phenotypic variation by increasing transposable element mobility.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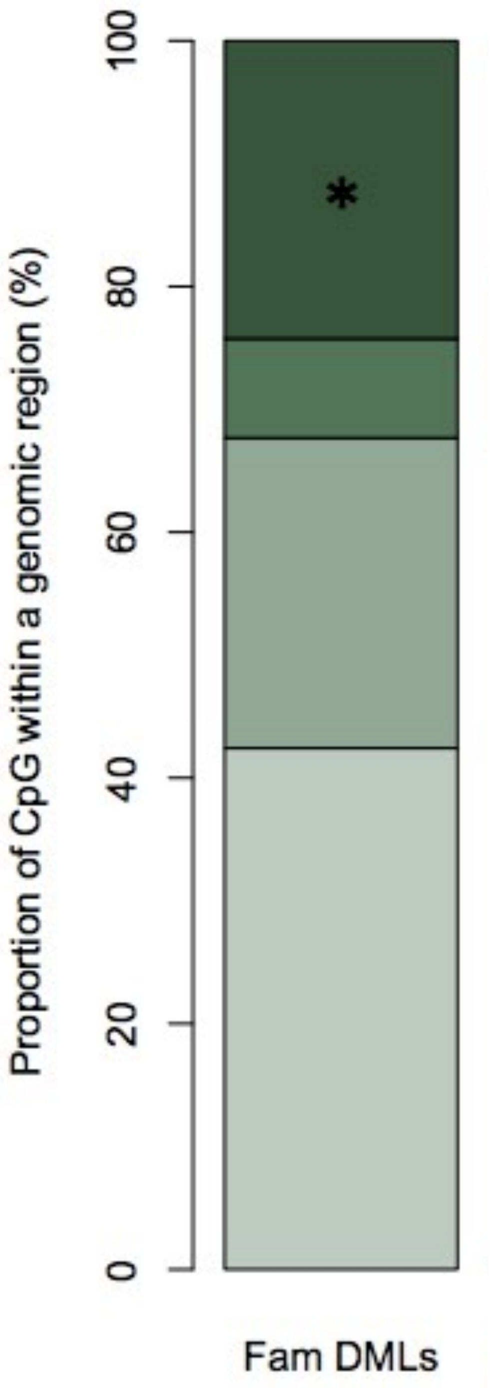

Assumes some form of random process occurring during gametogenesis?

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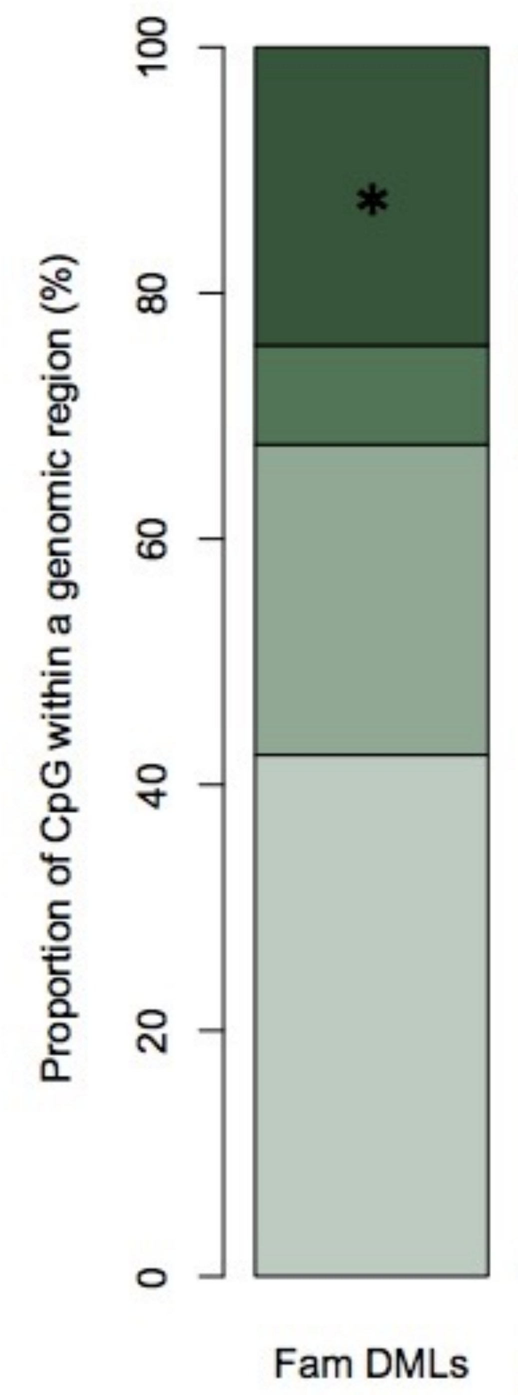


che625 / **olson-ms-nb**

IPython Notebook for downloading and analyzing data the manusript: "Indication of family-specific DNA methylation patterns in developing oysters"

bioRix preprint - http://dx.doi.org/10.1101/012831

To execute the IPython Notebook in its entirety you will need:

- IPython - install instructions
- BSMAP - install instructions
- bedtools - install instructions
- R - install instructions
- rpy2 (interface to R from Python) - install instructions

Epigenetic variation 1

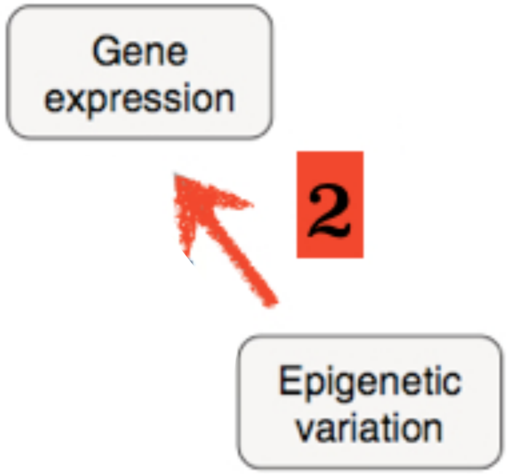
Summary

- Sparsely (~16 %) methylated genome

- Limited variation between cell type

- Gene body methylation correlated with function

- Evidence indicates DMRs are predominant in transposable elements

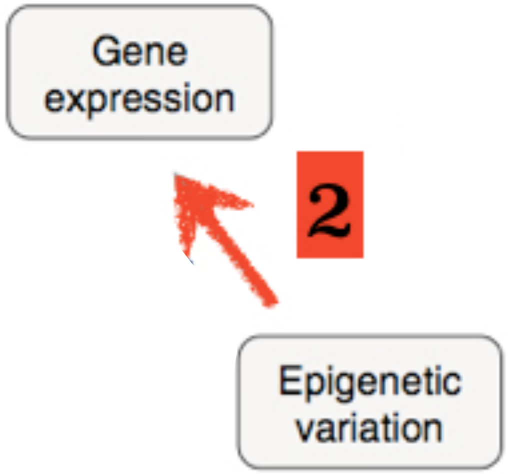


Gene expression

2

Epigenetic variation

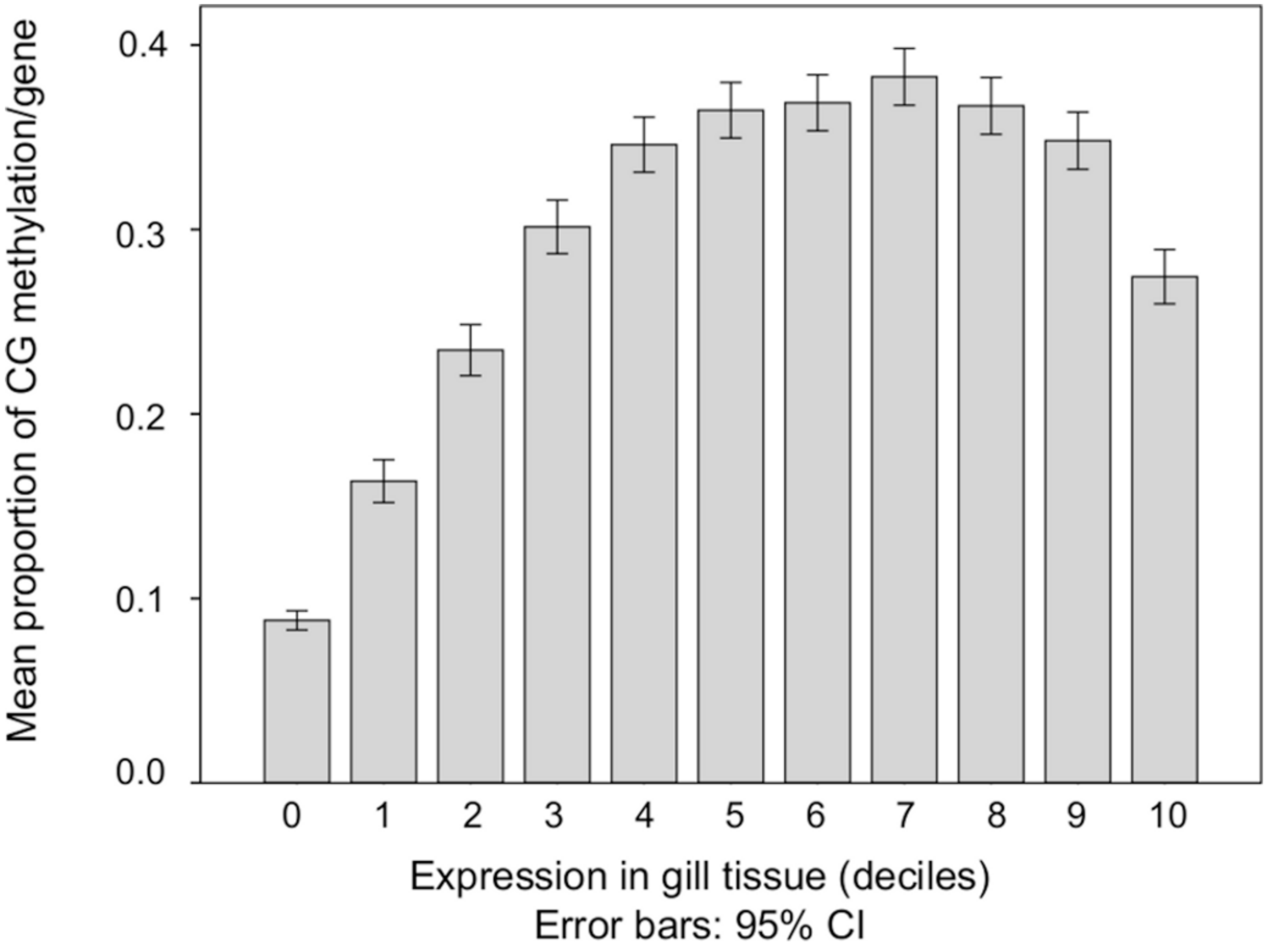
Function?



Gene expression

2

Epigenetic variation



PeerJ

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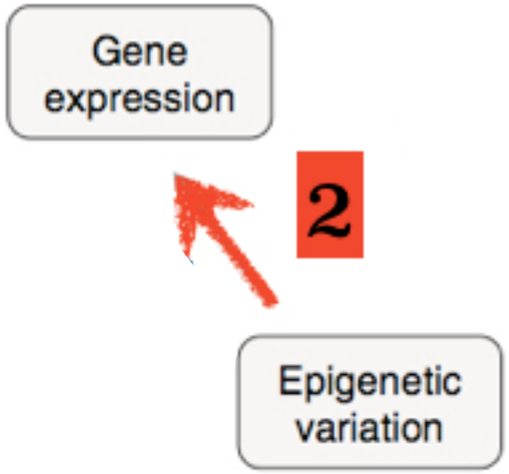

Gene expression

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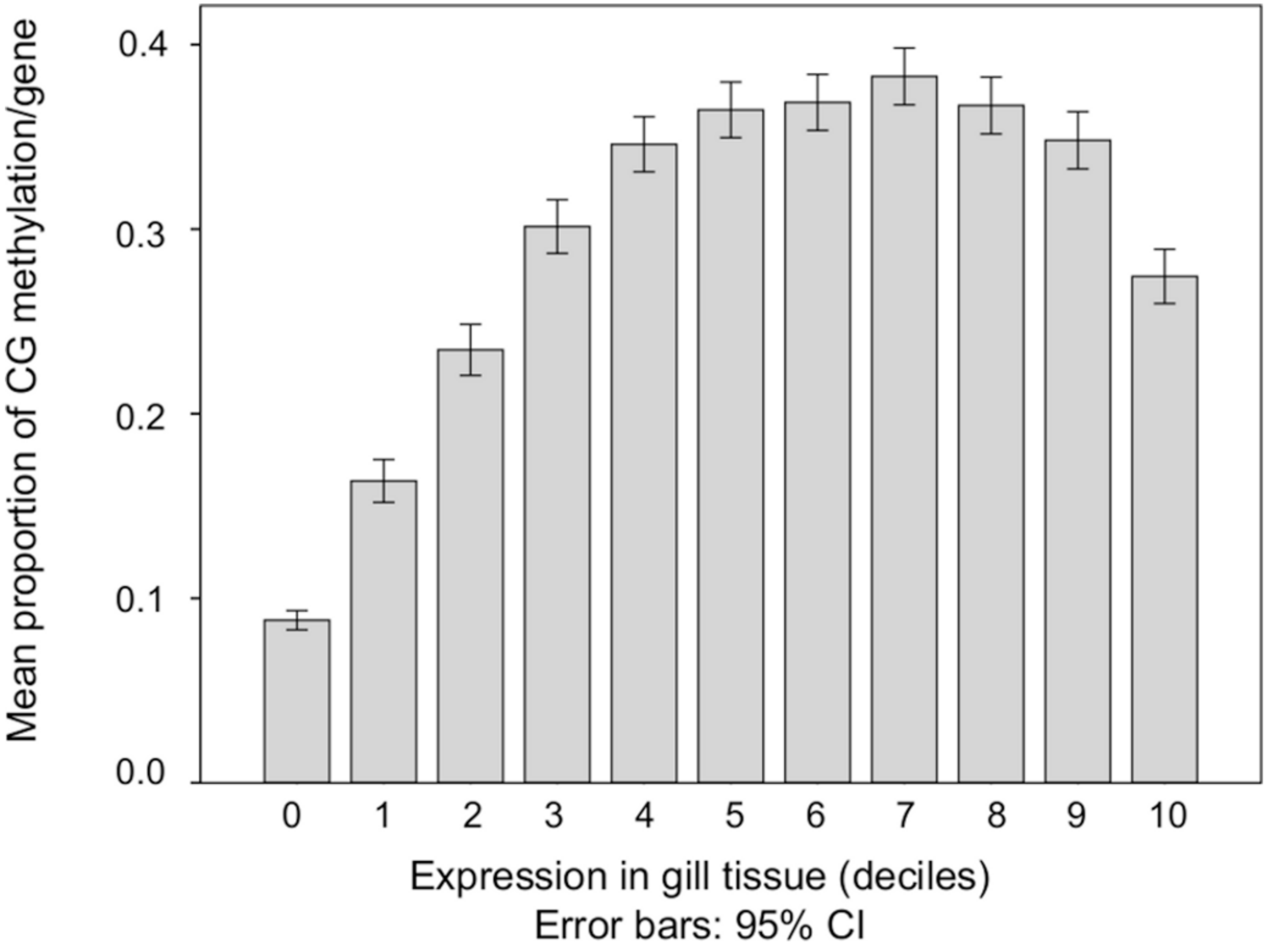

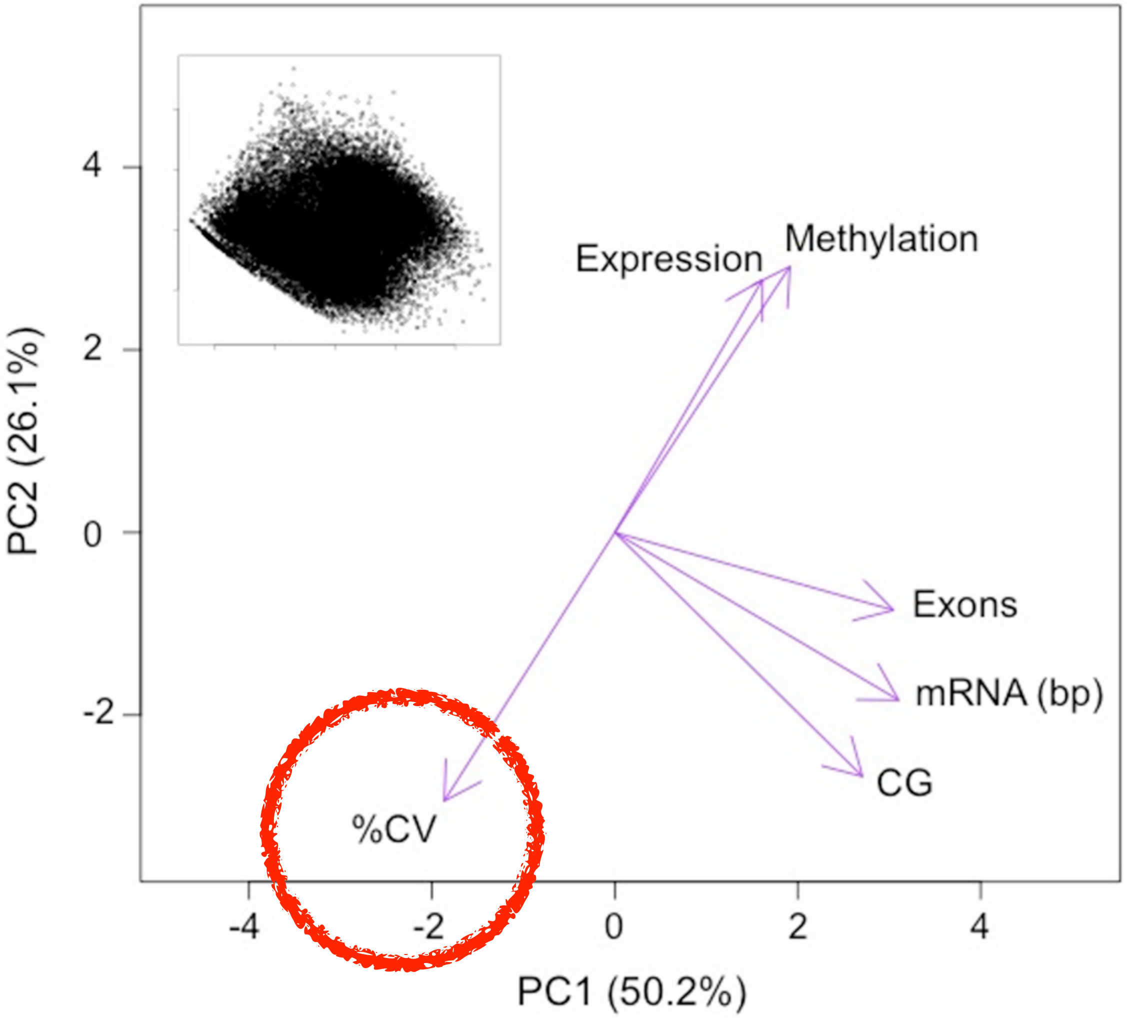

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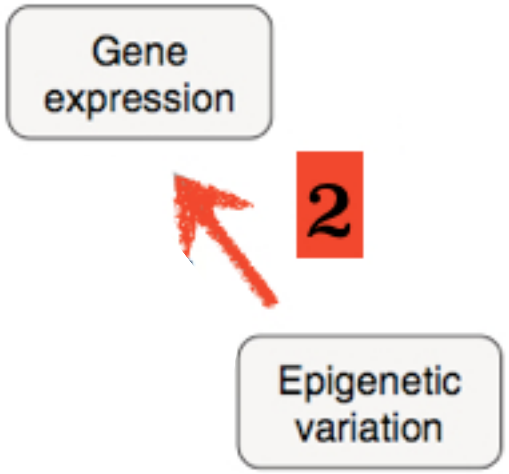
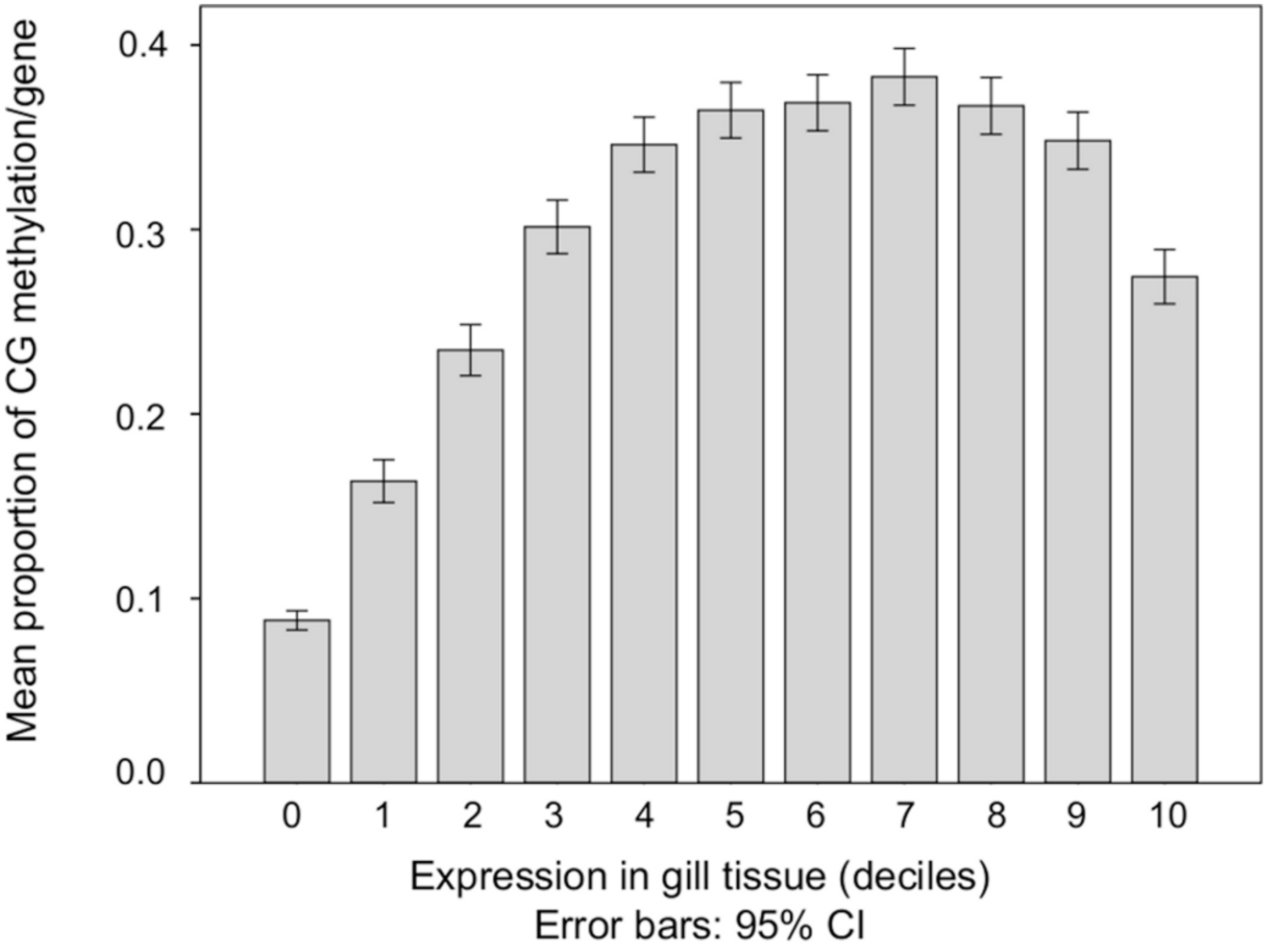
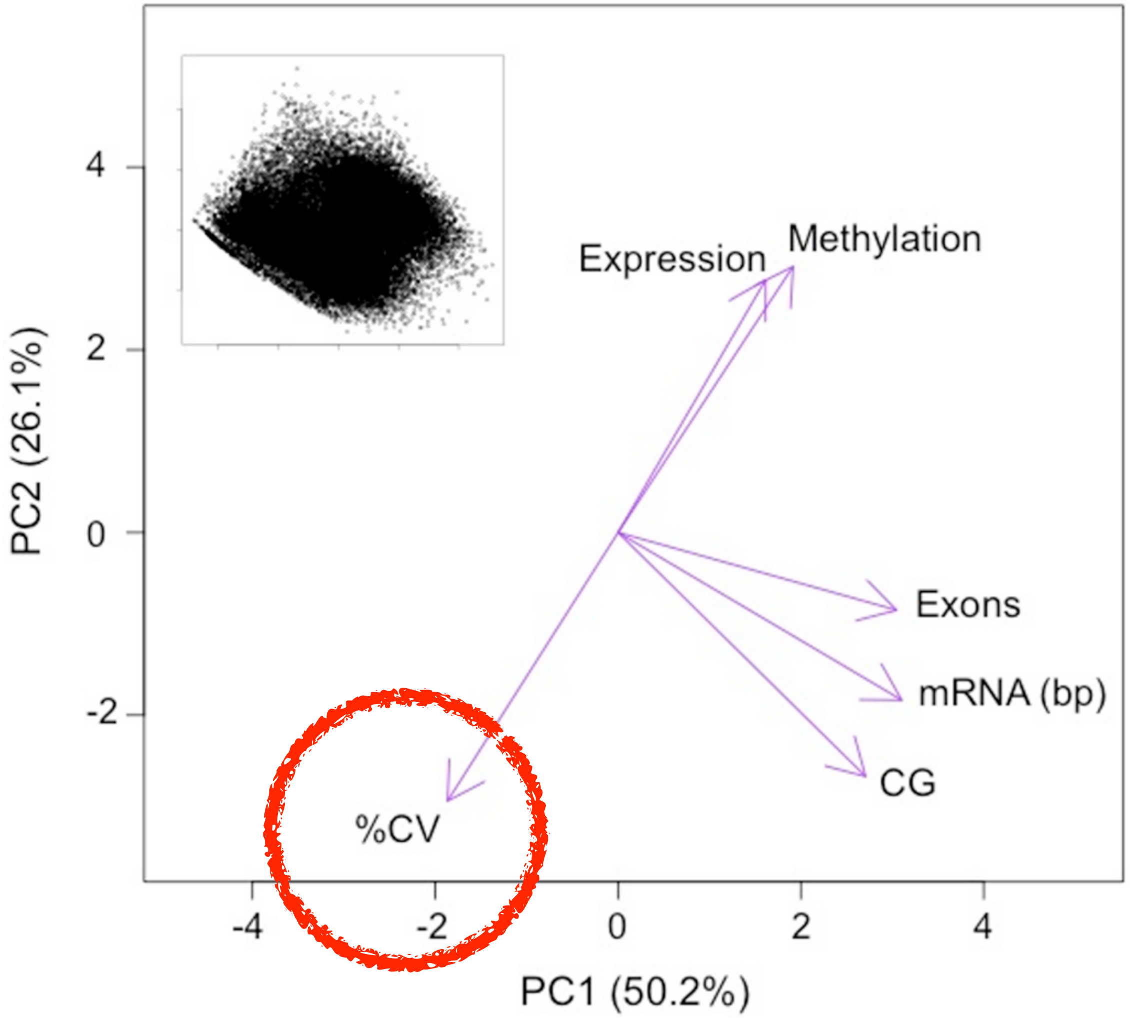


Theory: **Does not** influence expression level but rather alternative splicing.





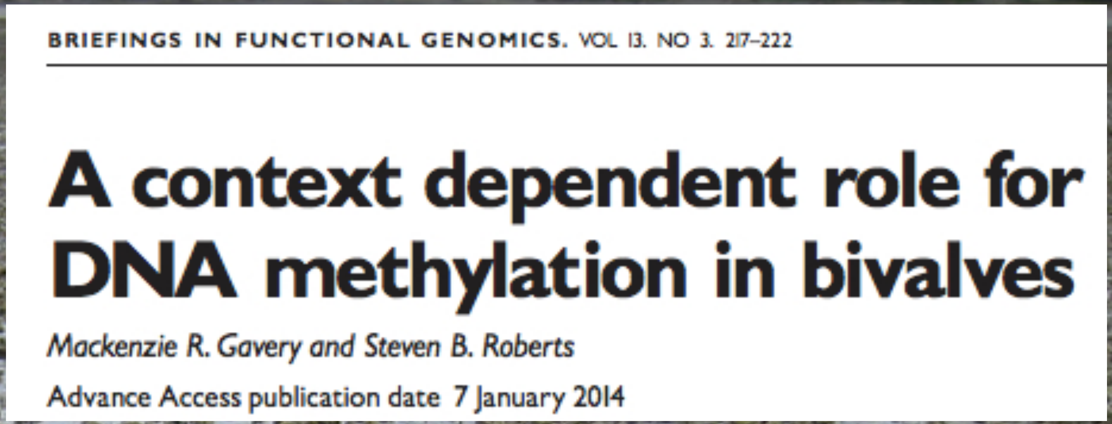
PeerJ

Predominant intragenic methylation is associated with gene expression characteristics in a bivalve mollusc

Mackenzie R. Gavery and Steven B. Roberts

School of Aquatic and Fishery Sciences, University of Washington, Seattle, WA, USA

What?



BRIEFINGS IN FUNCTIONAL GENOMICS. VOL 13. NO 3. 217–222

A context dependent role for DNA methylation in bivalves

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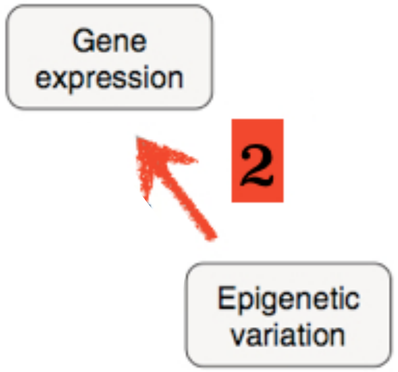
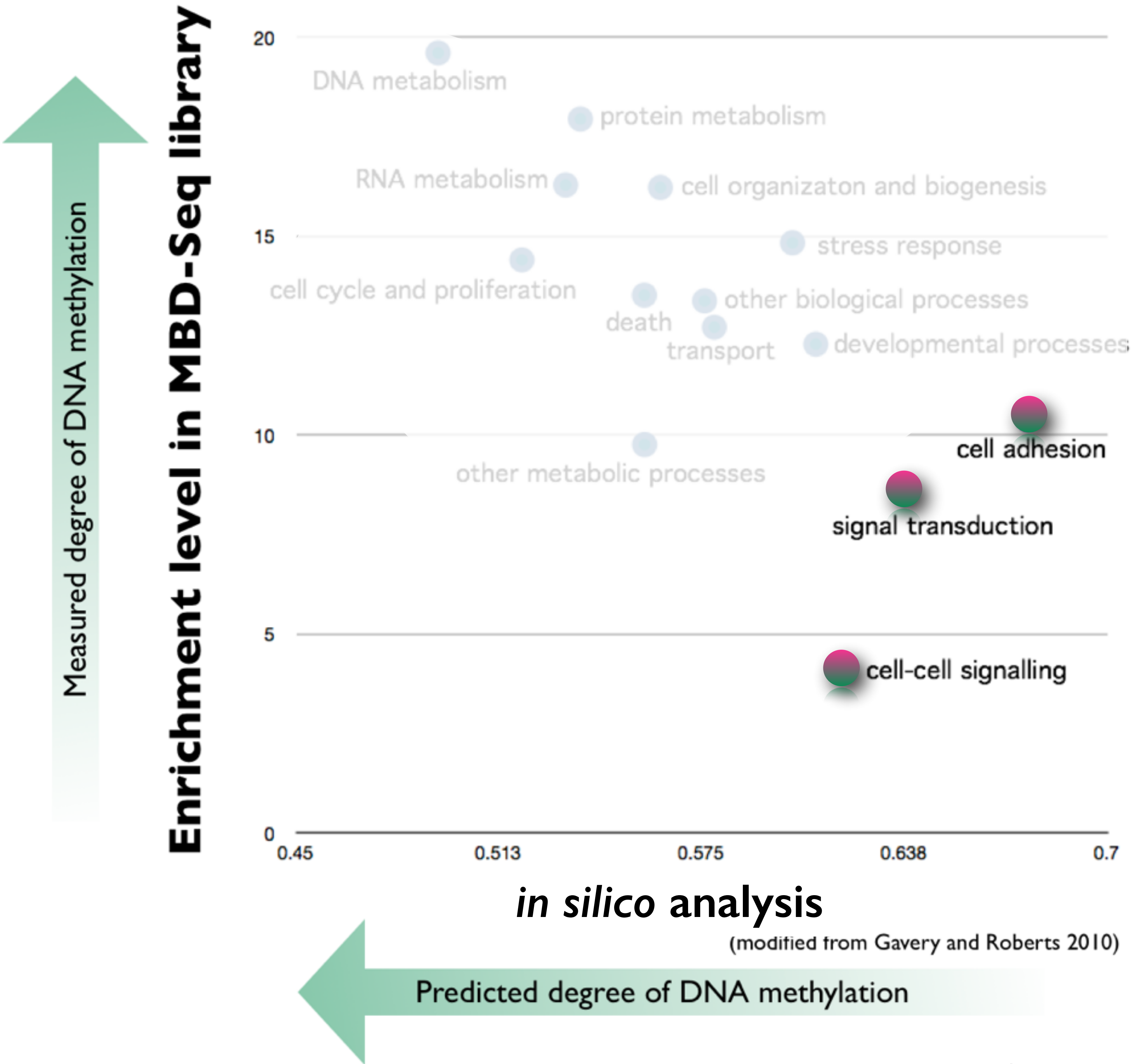
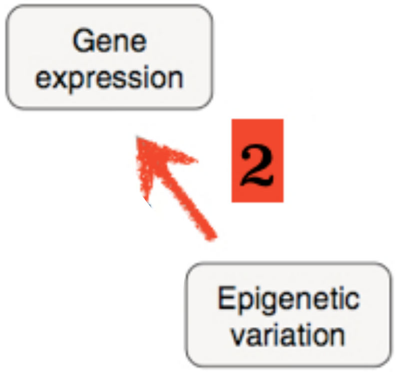
In species that experience a diverse range of environmental conditions, processes have evolved to increase the number of potential phenotypes in a population in order to improve the chances for an individual's survival.





(modified from Gavery and Roberts 2010)

Roberts and Gavery 2012

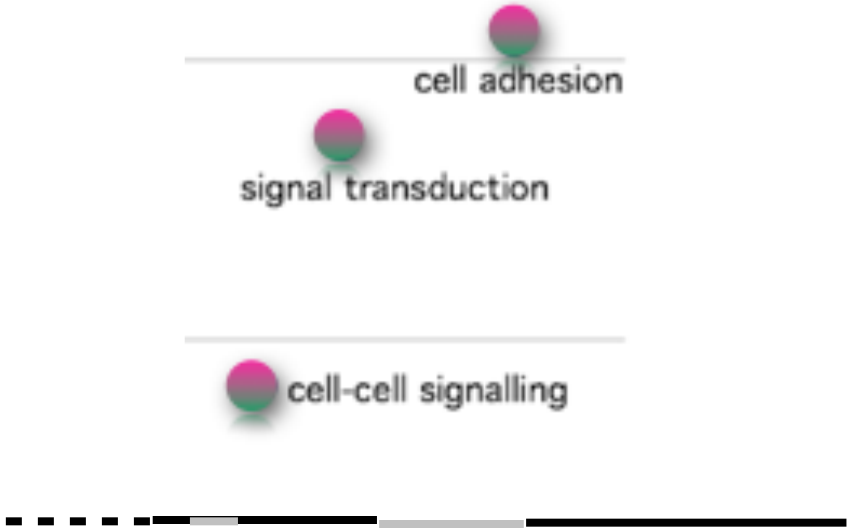


Gene expression

2

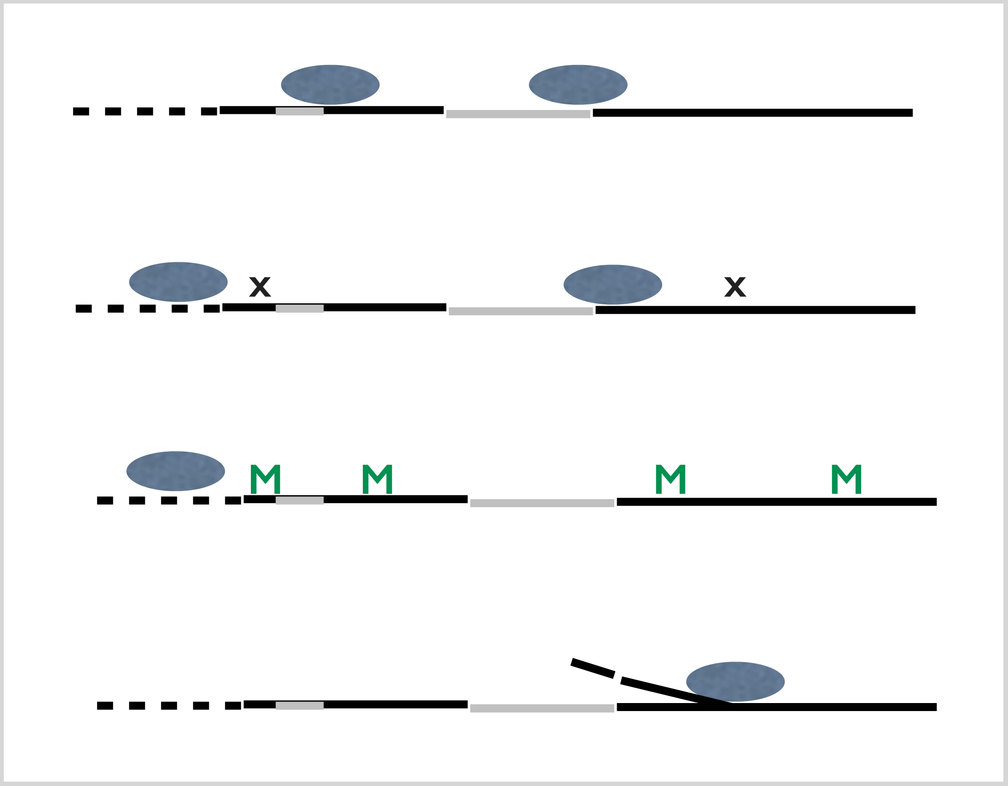
Epigenetic variation

Transcriptional opportunities



sparse methylation

tissue / temporal specific and inducible genes



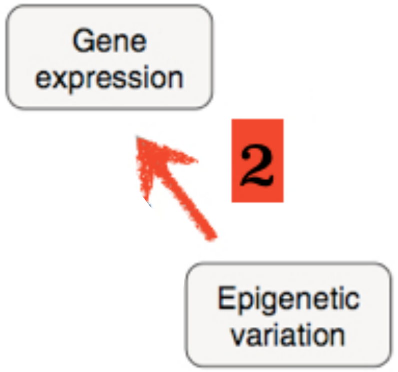
alternative start sites

sequence mutation
change AA, premature stop codon

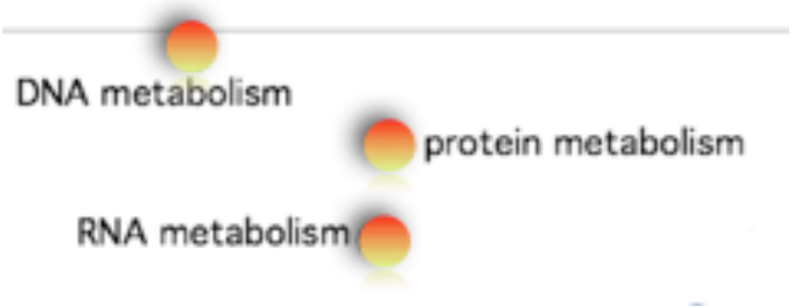
conventional transcription
transient methylation

alternate transcript
exon skipping

Roberts and Gavery 2012



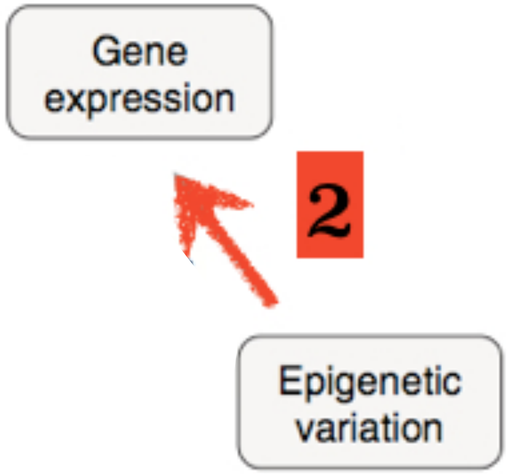
Transcriptional opportunities



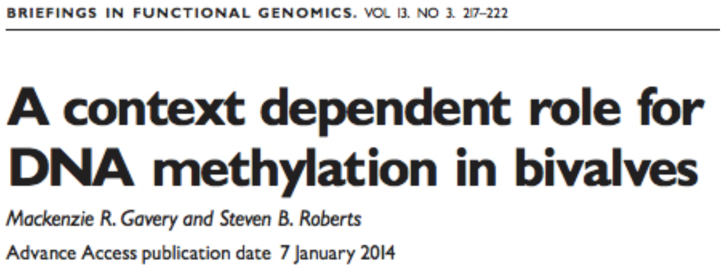
germline methylation

ubiquitously expressed,
critical genes

conventional transcription
5’ UTR promotor



Stochastic Variation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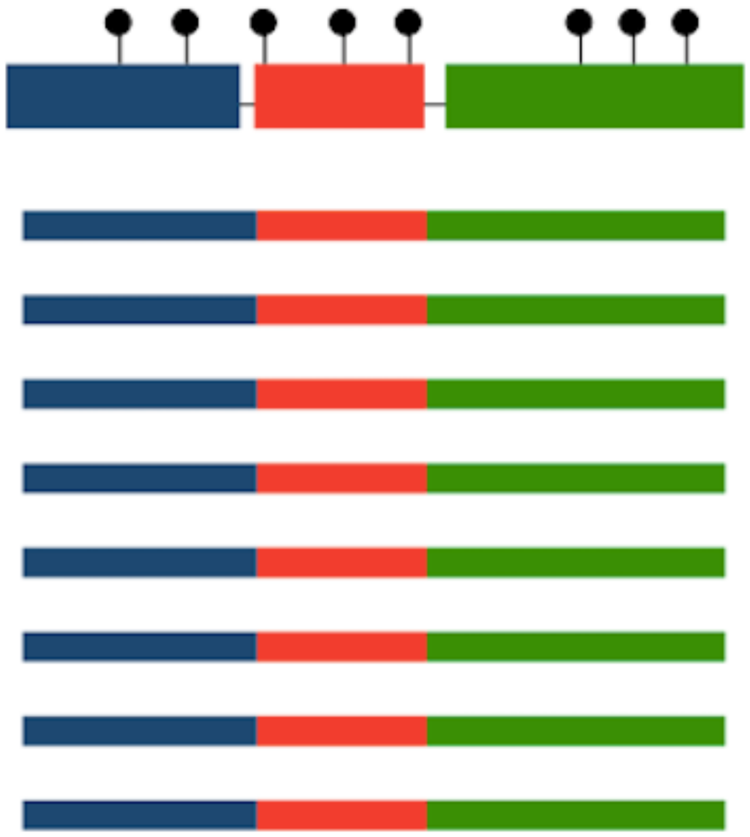
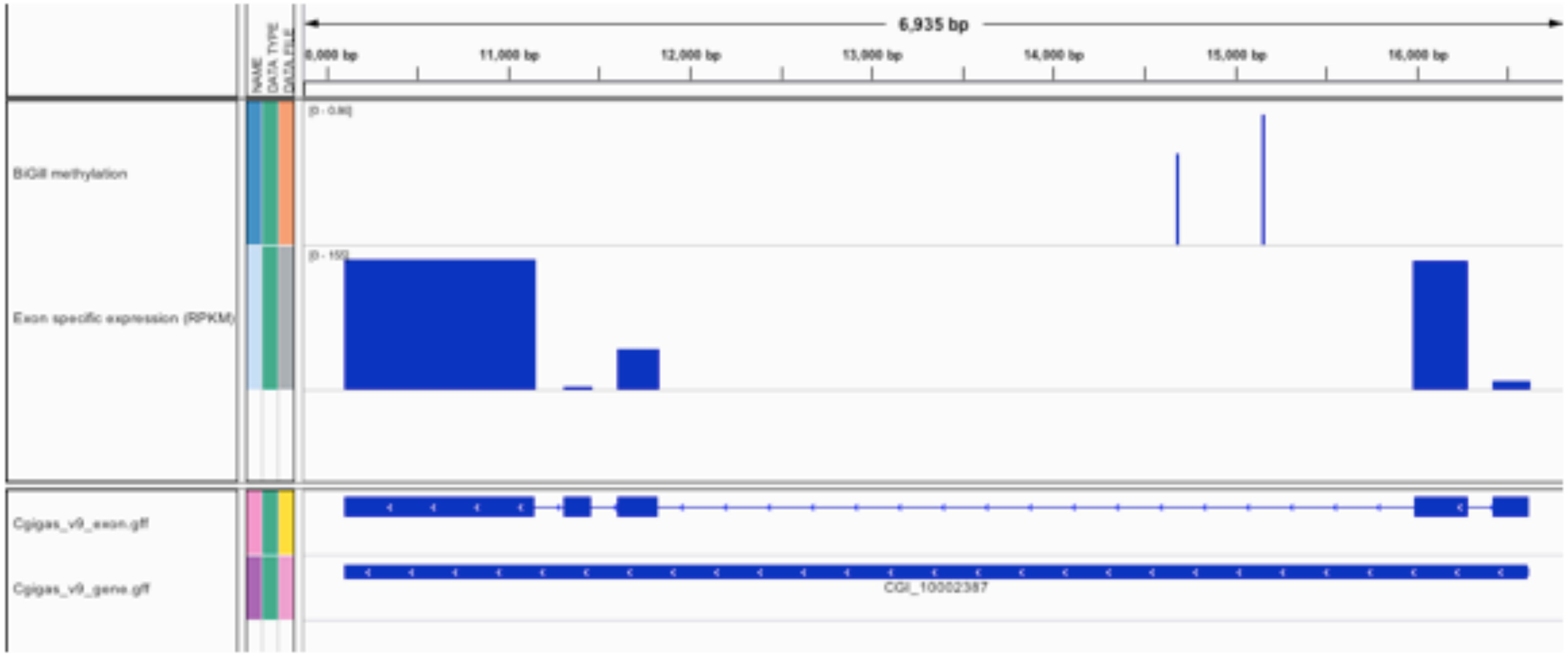


housekeeping

response to change

response to change

Heat shock 70 kDa protein 12A

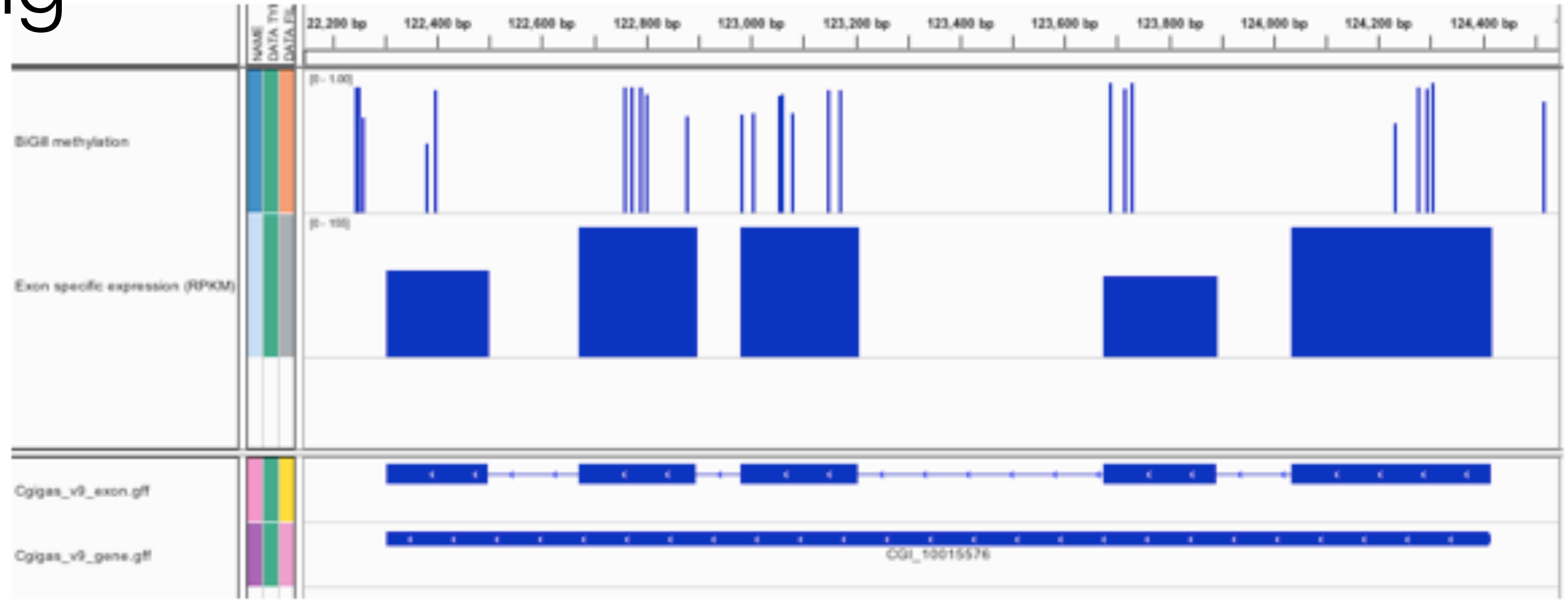


avg exp
199

%meth
2%

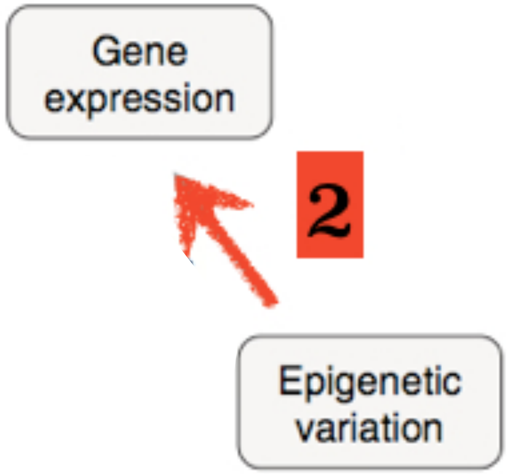
housekeeping

Tektin-2

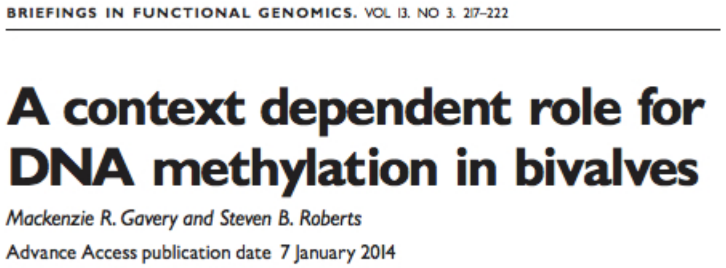


avg exp
197

%meth
91%



Targeted Regulation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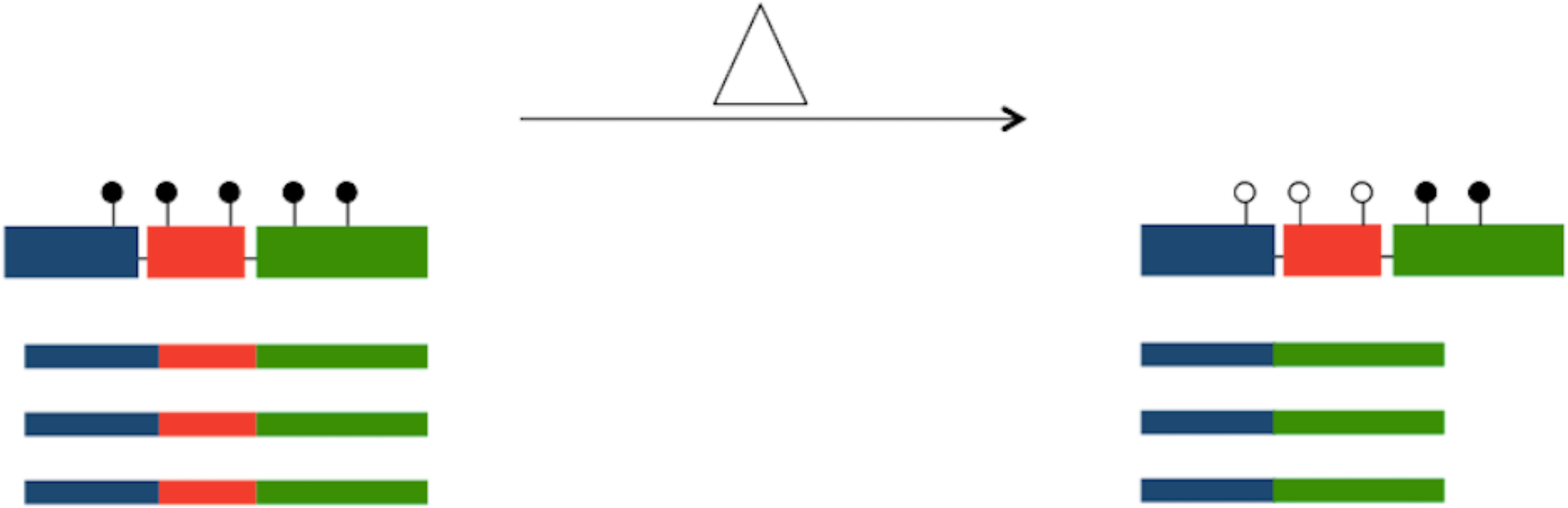
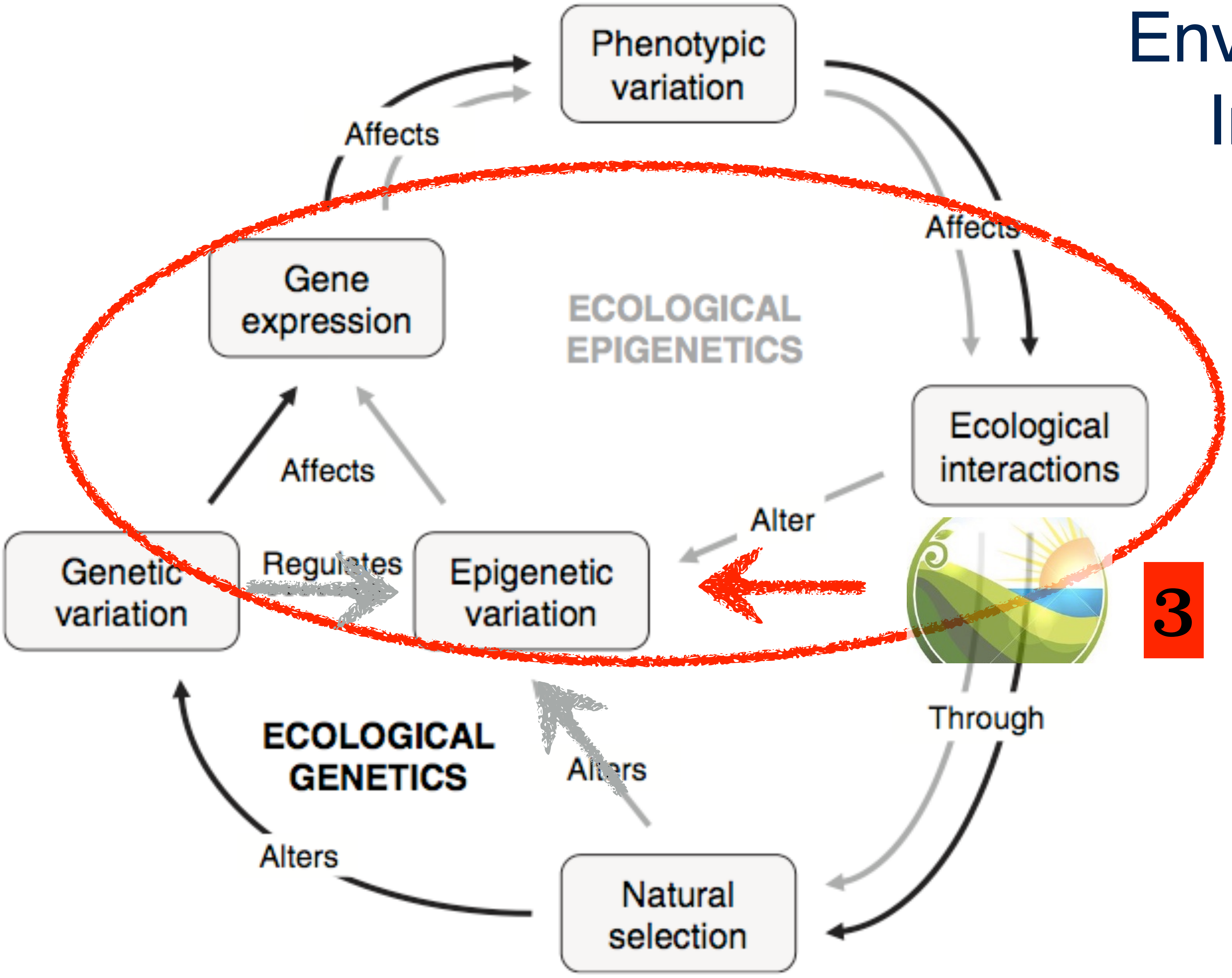


Environmental Influence



modified from

Ecology Letters, (2008) **11:** 106–115 doi: 10.1111/j.1461-0248.2007.01130.x

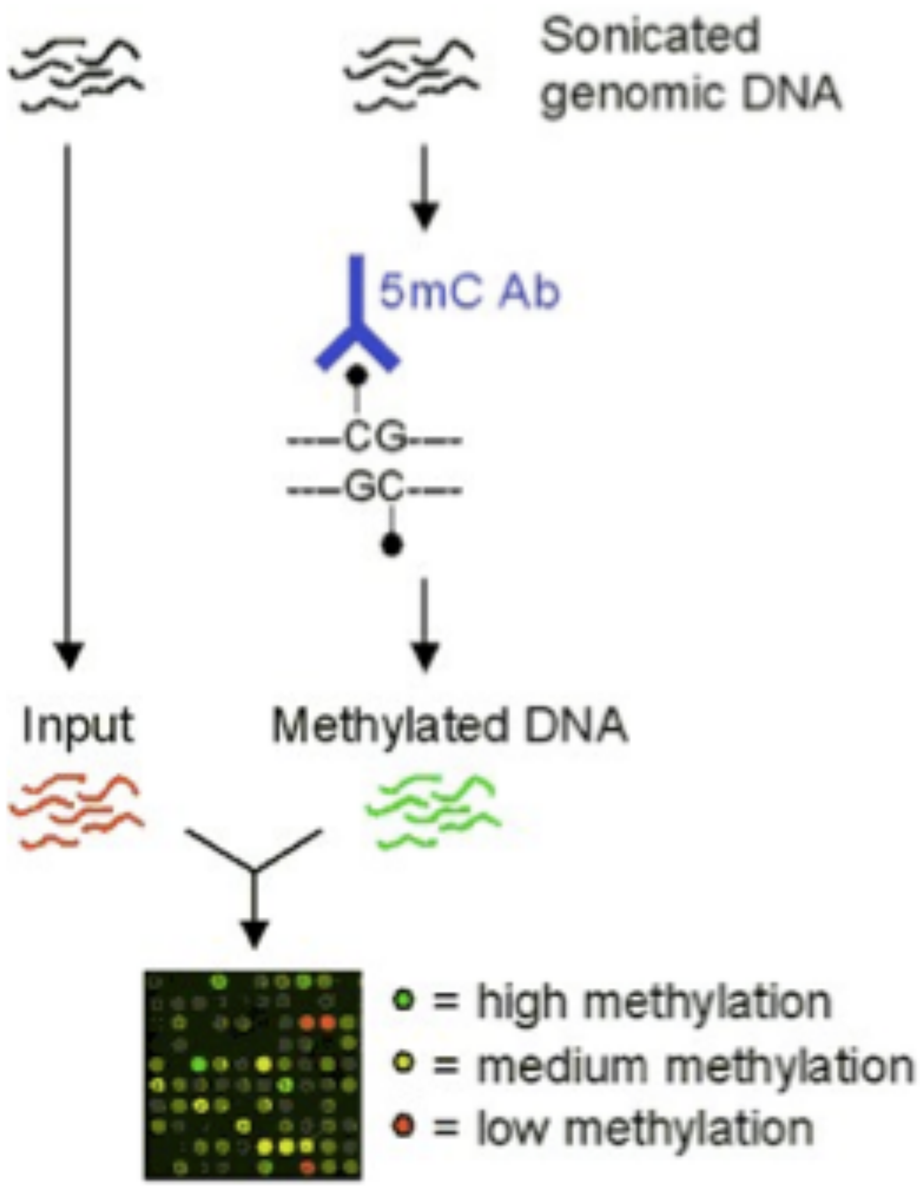
IDEA AND PERSPECTIVE

Epigenetics for ecologists

Oliver Bossdorf,[1]* Christina L. Richards[2] and Massimo Pigliucci[3]

Very new data

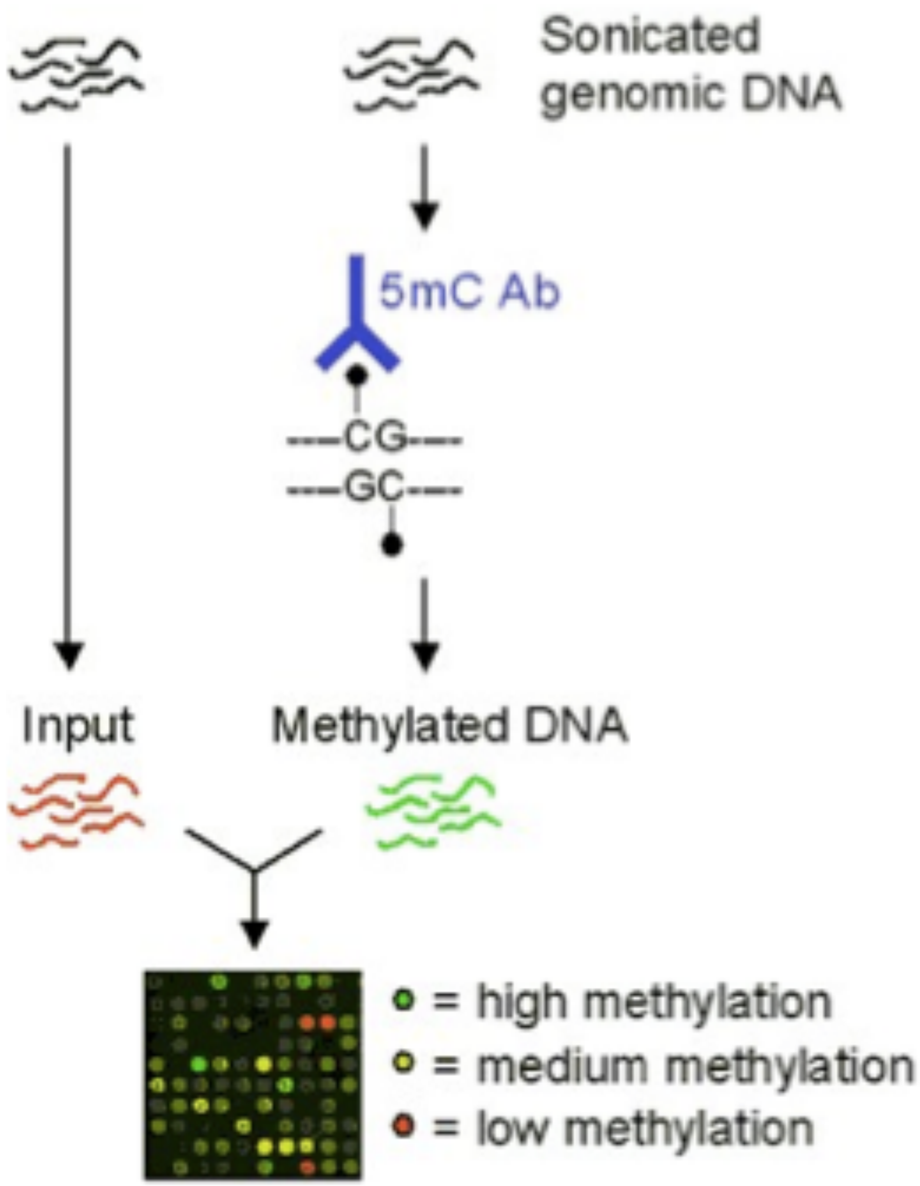
Environmental impact (Estrogens)



- 96 regions that were hypermethylated in EE2
  - – 90 are in genes
  - – 52 of these cross exon/intron boundary another
  - – 32 are in introns
  - – 6 are just in exons
- 287 regions that were hypomethylated in EE2
  - – 256 are in genes
  - – 138 cross exon/intron boundary
  - – 114 are in introns only and
  - – 4 are just in exons

Very new data

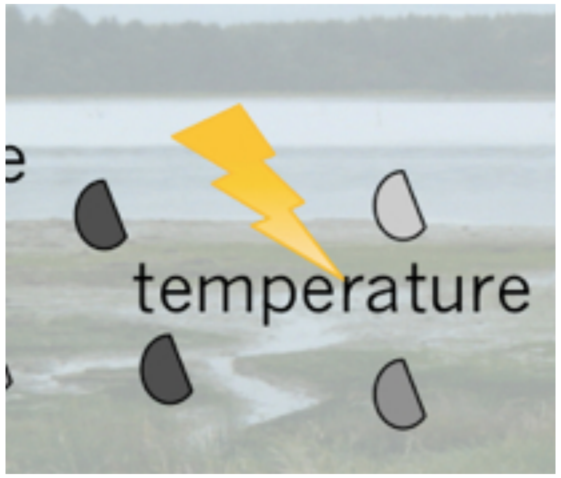
Environmental impact (Estrogens)



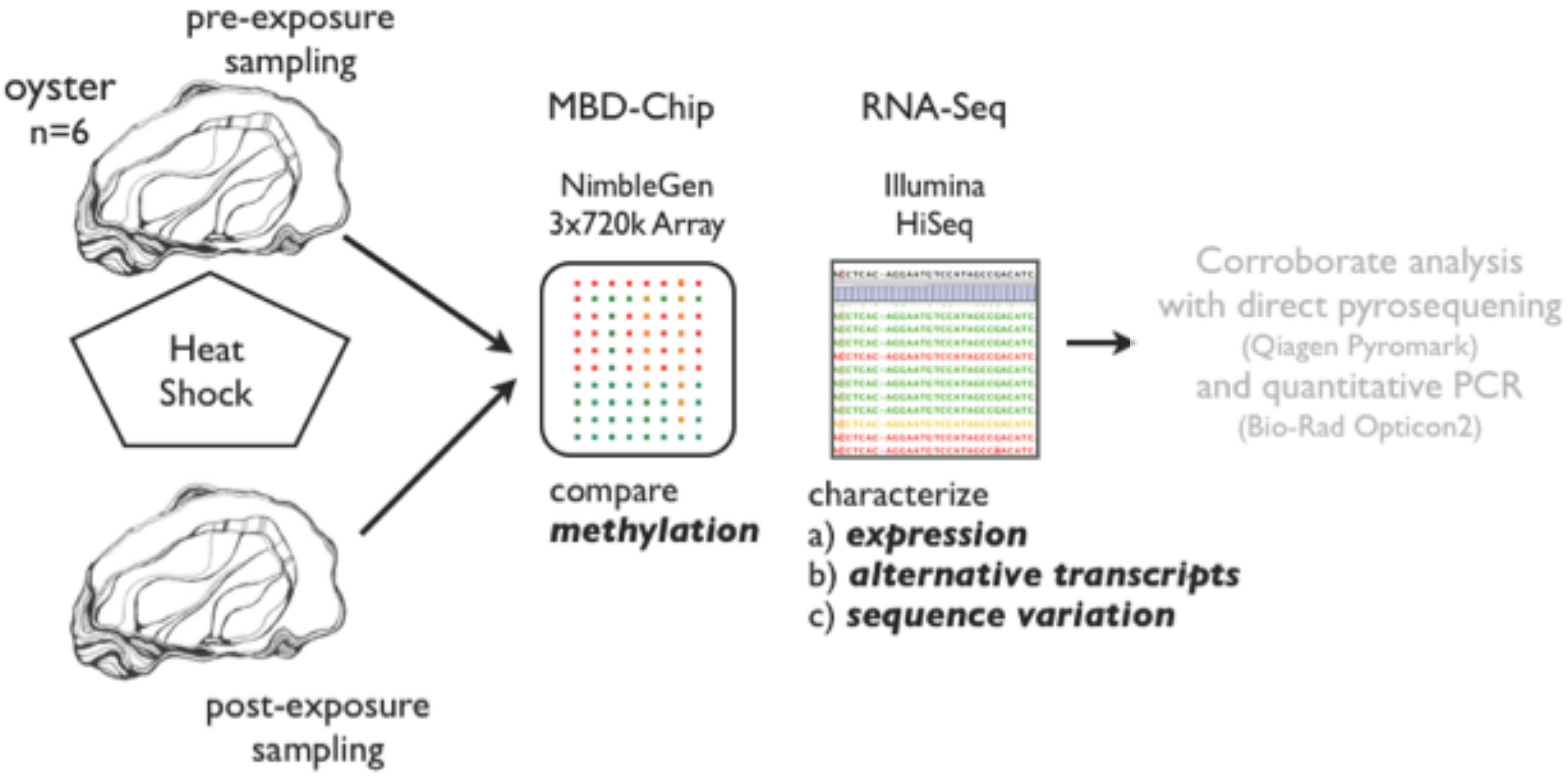
Exposure results in significant hypomethylation

Very new data

Environment and gene expression

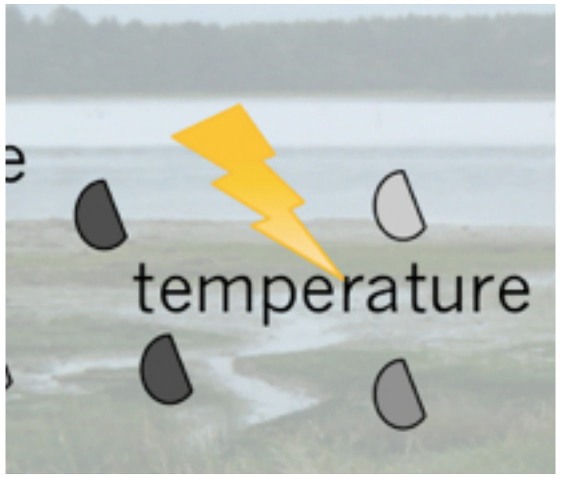


stochastic or targeted?



Very new data

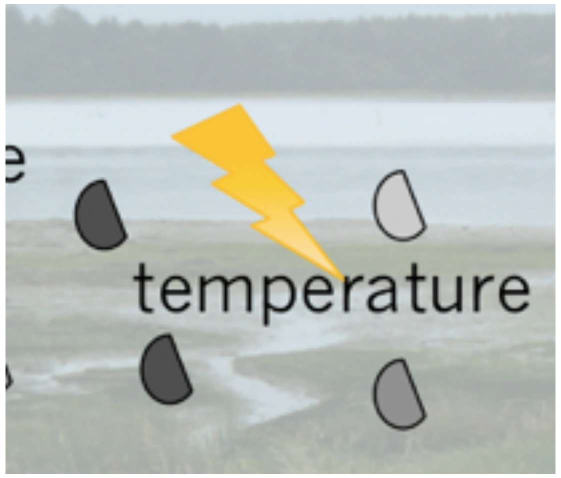
Environment and gene expression



stochastic or targeted?

Oyster	Hypo-methylated	Hyper-methylated
2	7224	2803
4	6560	3587
6	7645	4044

Very new data
Environment and gene expression

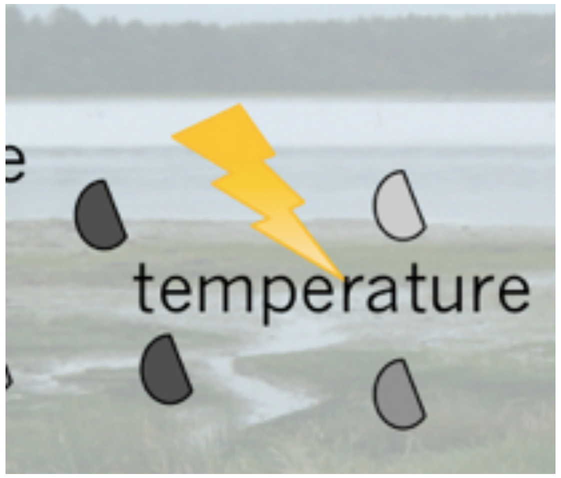


stochastic or targeted?

Oyster	Hypo-methylated	Hyper-methylated
2	7224	2803
4	6560	3587
6	7645	4044

No obvious association with genome feature including *differentially expressed genes*

Very new data
Environment and gene expression

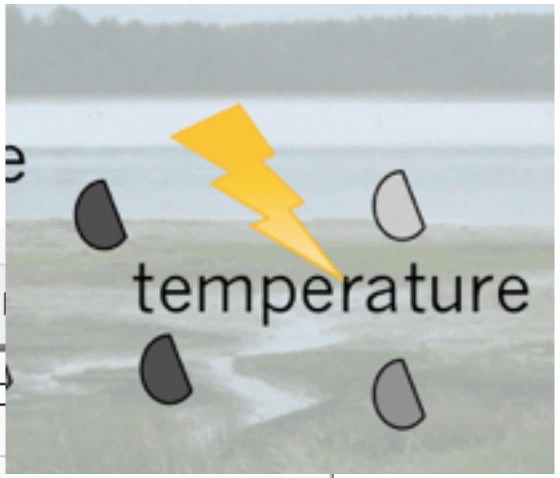


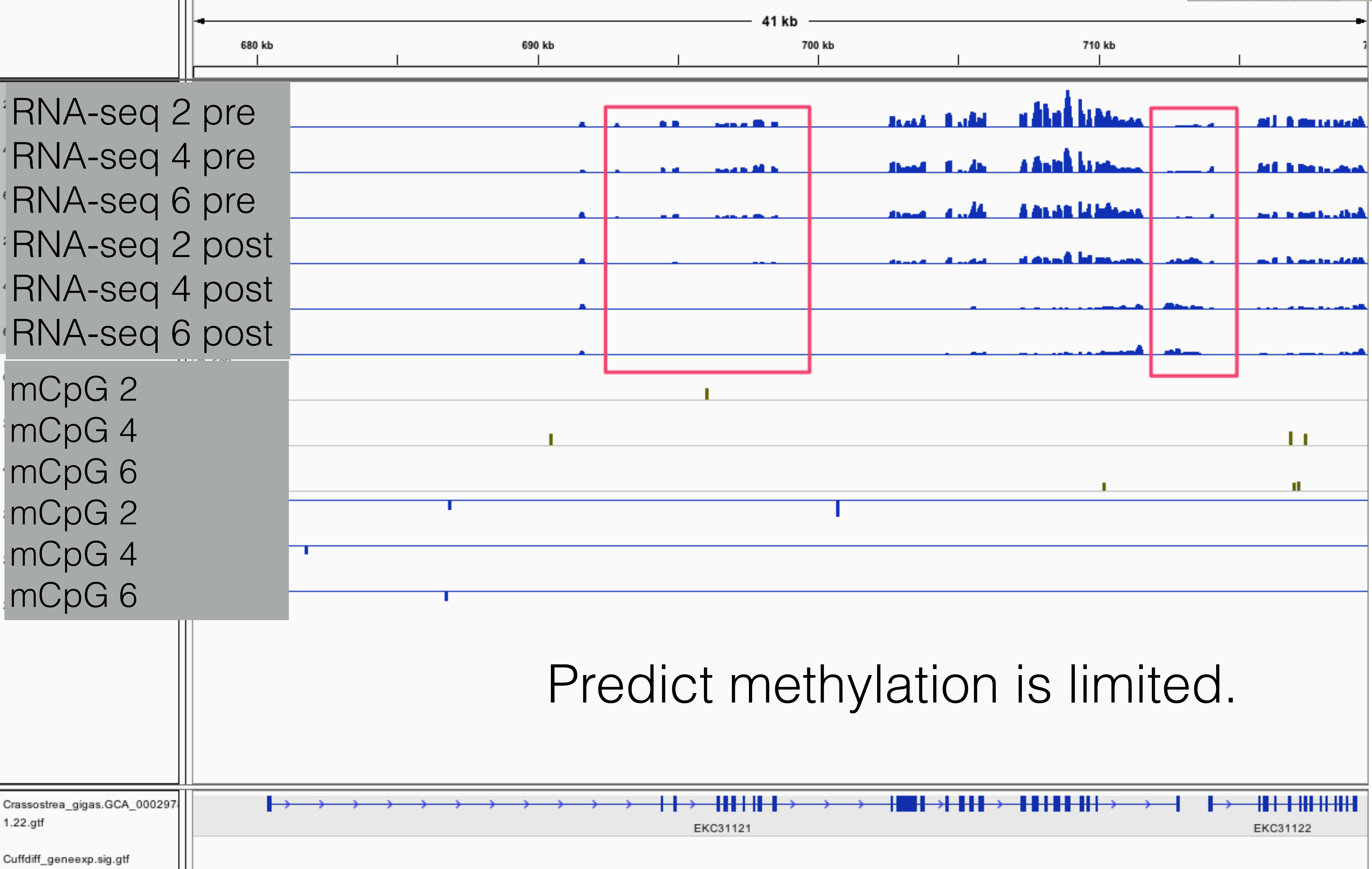
stochastic or targeted
or ..?

Oyster	Hypo-methylated	Hyper-methylated
2	7224	2803
4	6560	3587
6	7645	4044

Changes in methylation
(either direction)
are more prevalent
in introns, repeats,
and
transposable elements.

Very new data

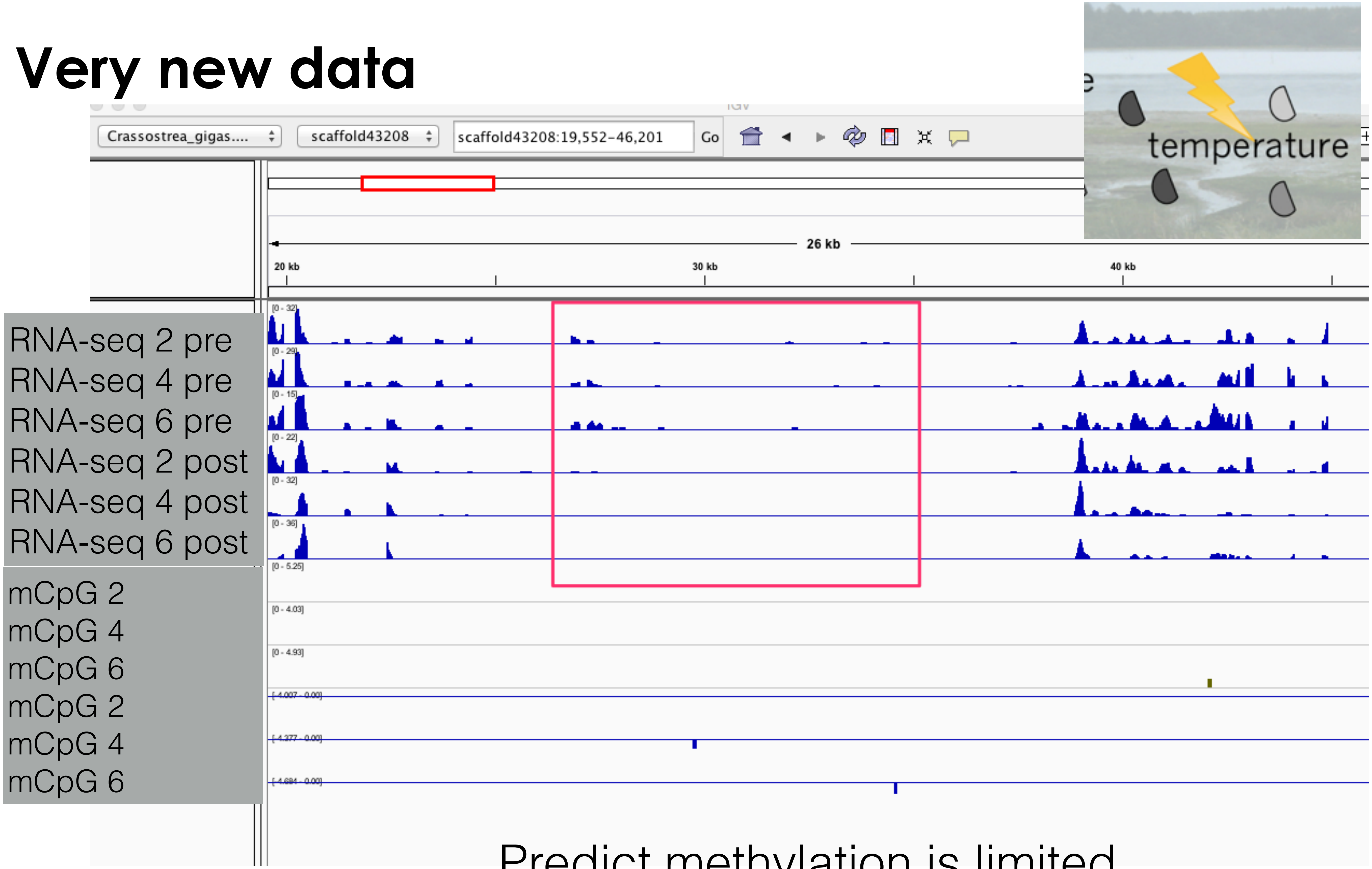




scaffold1009:677,703-719,650

Predict methylation is limited.

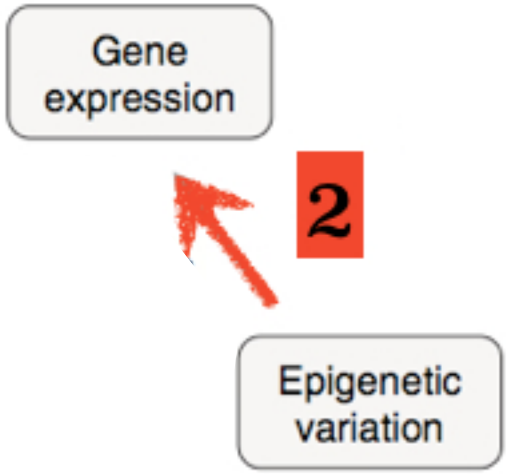
Very new data



RNA-seq 2 pre
RNA-seq 4 pre
RNA-seq 6 pre
RNA-seq 2 post
RNA-seq 4 post
RNA-seq 6 post

mCpG 2
mCpG 4
mCpG 6
mCpG 2
mCpG 4
mCpG 6

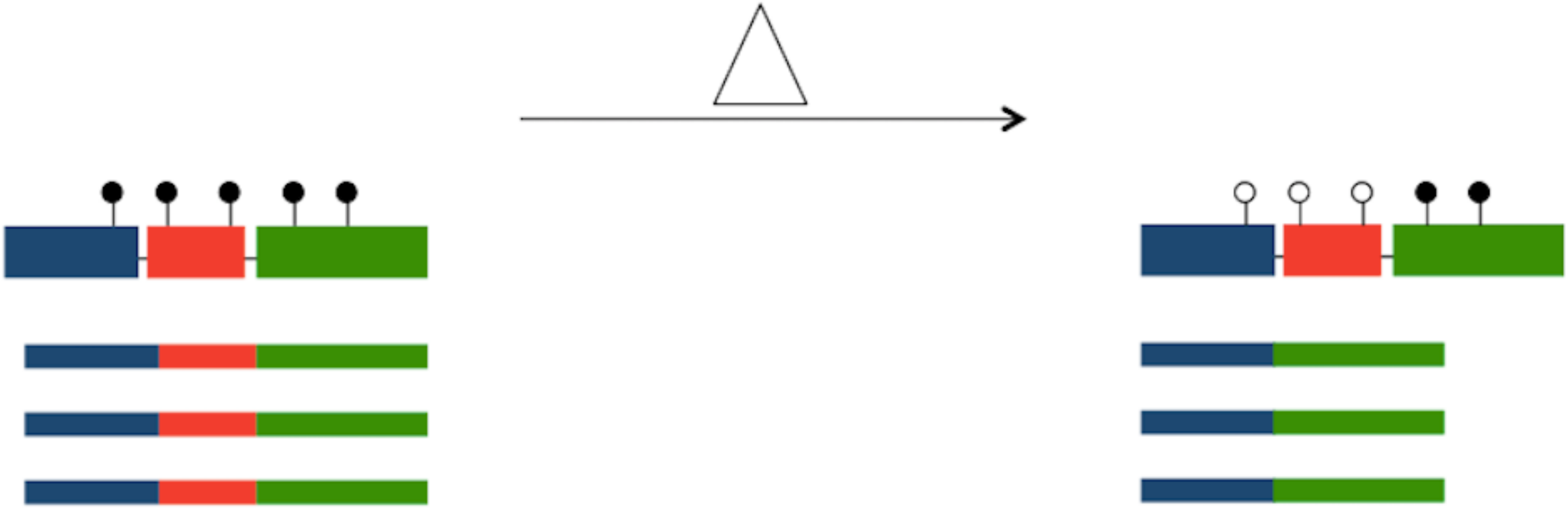
Predict methylation is limited.



Gene expression

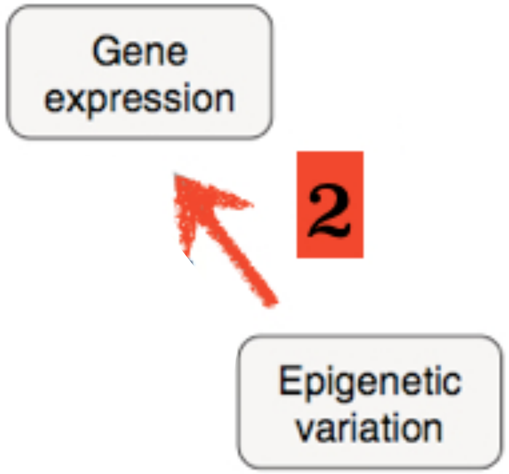
2

Epigenetic variation



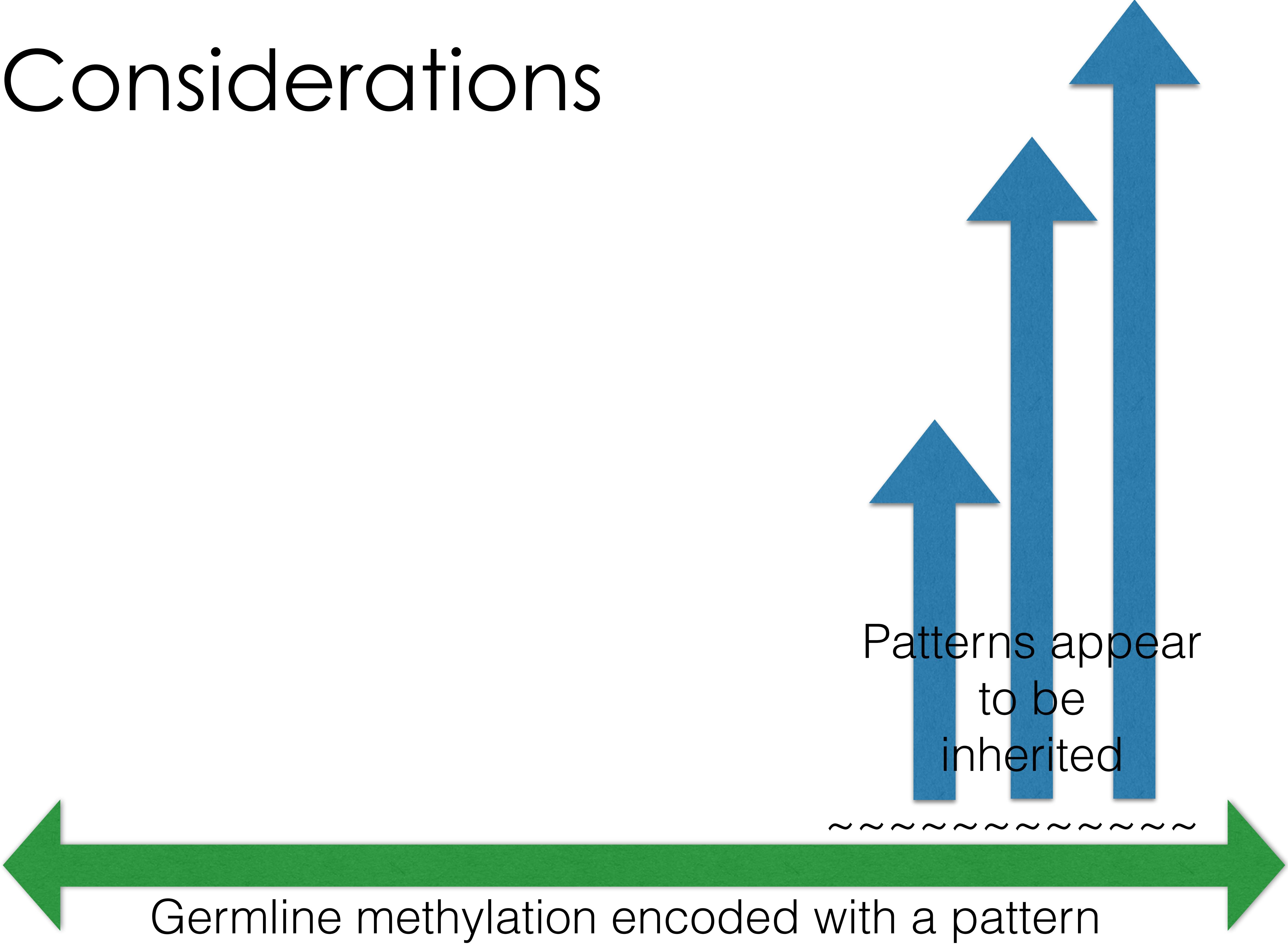
not in this experiment

not even consistent methylation changes at loci level



more questions….
interesting but what is controlling?

Considerations

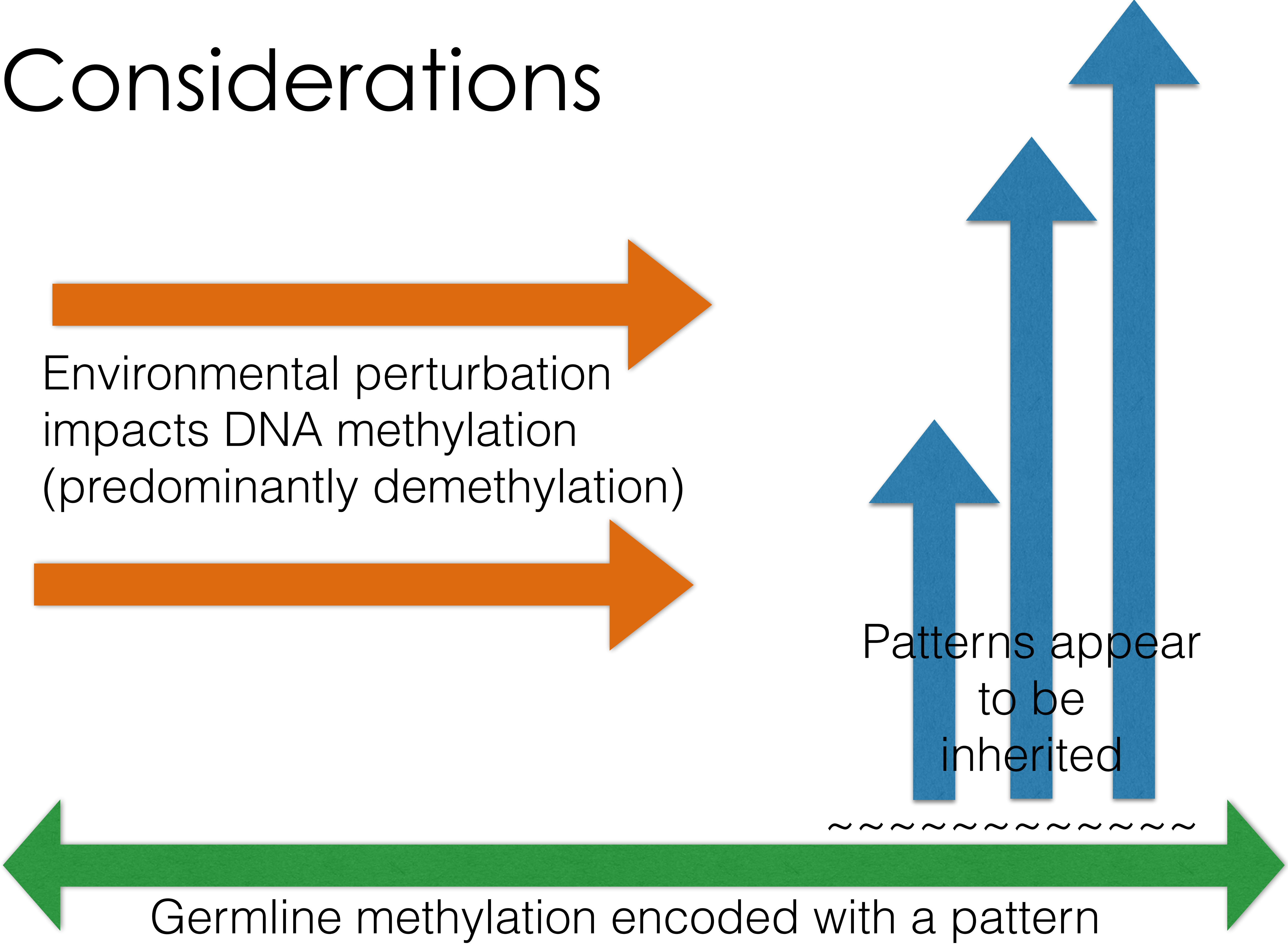


Patterns appear to be inherited

~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~

Germline methylation encoded with a pattern product of evolutionary forces

Considerations



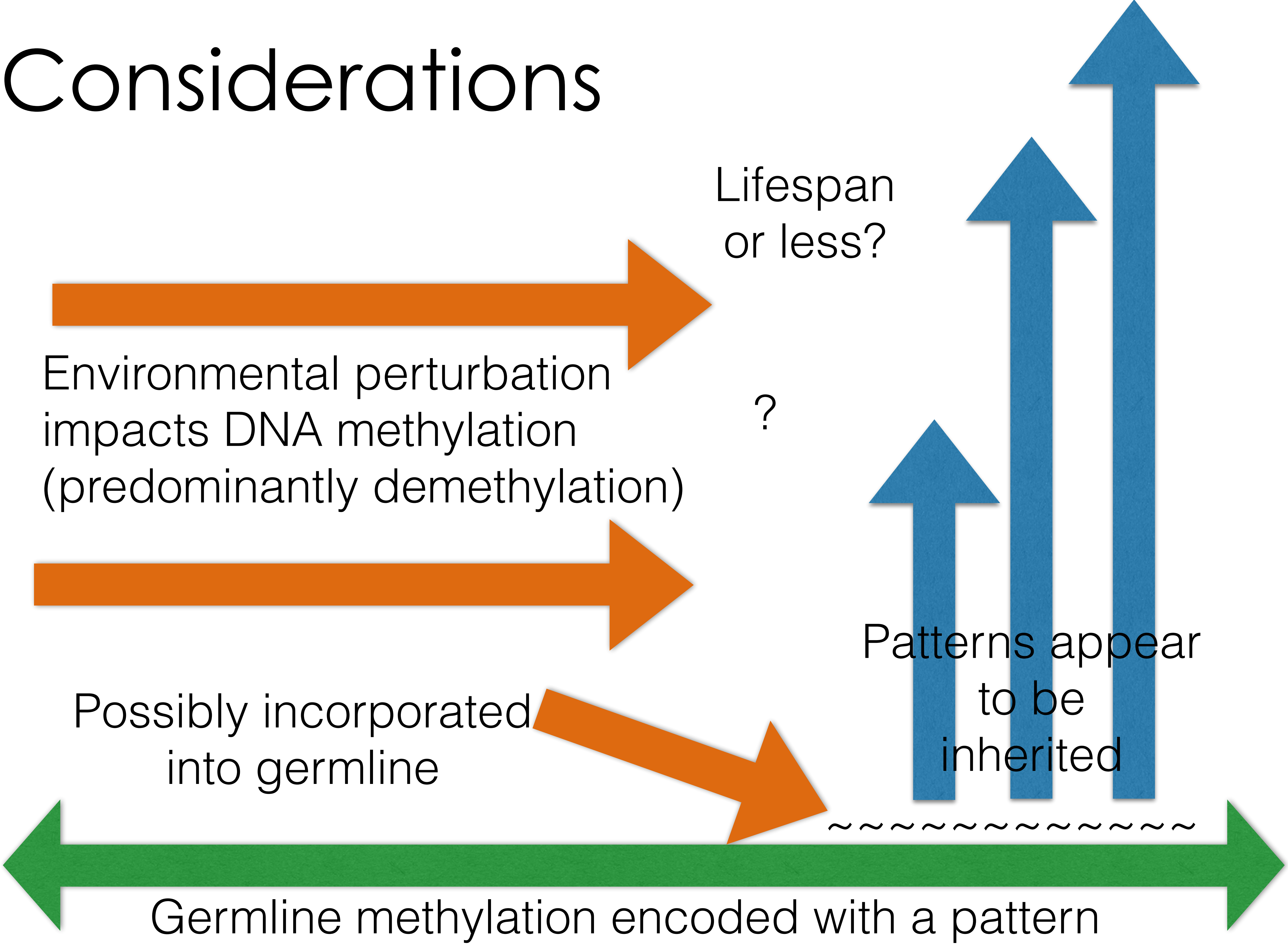
Environmental perturbation impacts DNA methylation (predominantly demethylation)

Patterns appear to be inherited

~~~~~~~~~~~~~~~

Germline methylation encoded with a pattern product of evolutionary forces
~~~~~~~~~~~~~~~

Considerations



Lifespan or less?

Environmental perturbation impacts DNA methylation (predominantly demethylation)

?

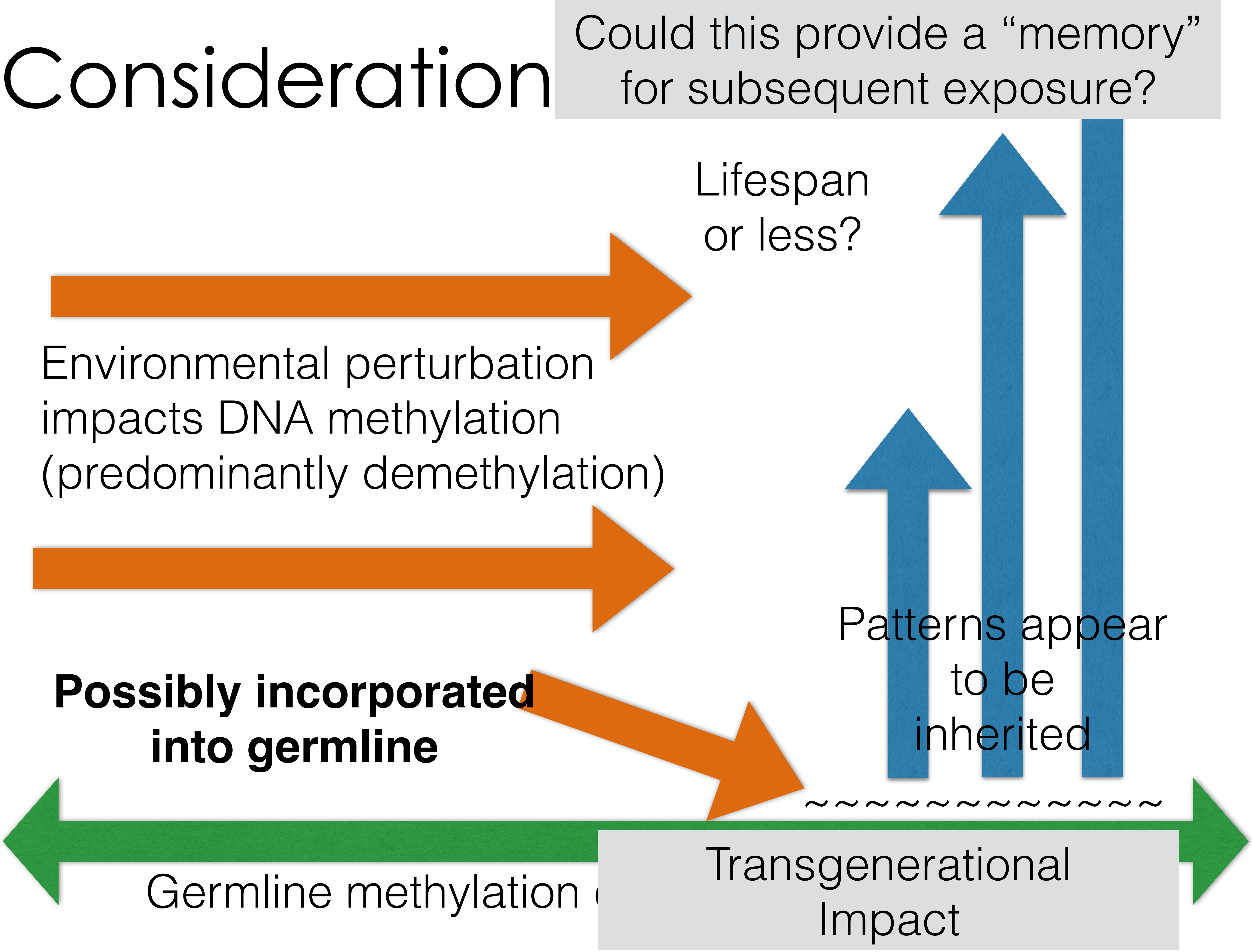
Possibly incorporated into germline

Patterns appear to be inherited

~~~~~~~~~~~~~~

Germline methylation encoded with a pattern
~~~~~~~~~~~~~~

Consideration



Could this provide a “memory” for subsequent exposure?

Lifespan
or less?

Environmental perturbation impacts DNA methylation (predominantly demethylation)

Possibly incorporated into germline

Patterns appear to be inherited

~~~~~~~~~~~~

Germline methylation

Transgenerational Impact
~~~~~~~~~~~~

Next Steps

Dig into the heat-shock data

Transposable Elements

Consider other epigenetic process

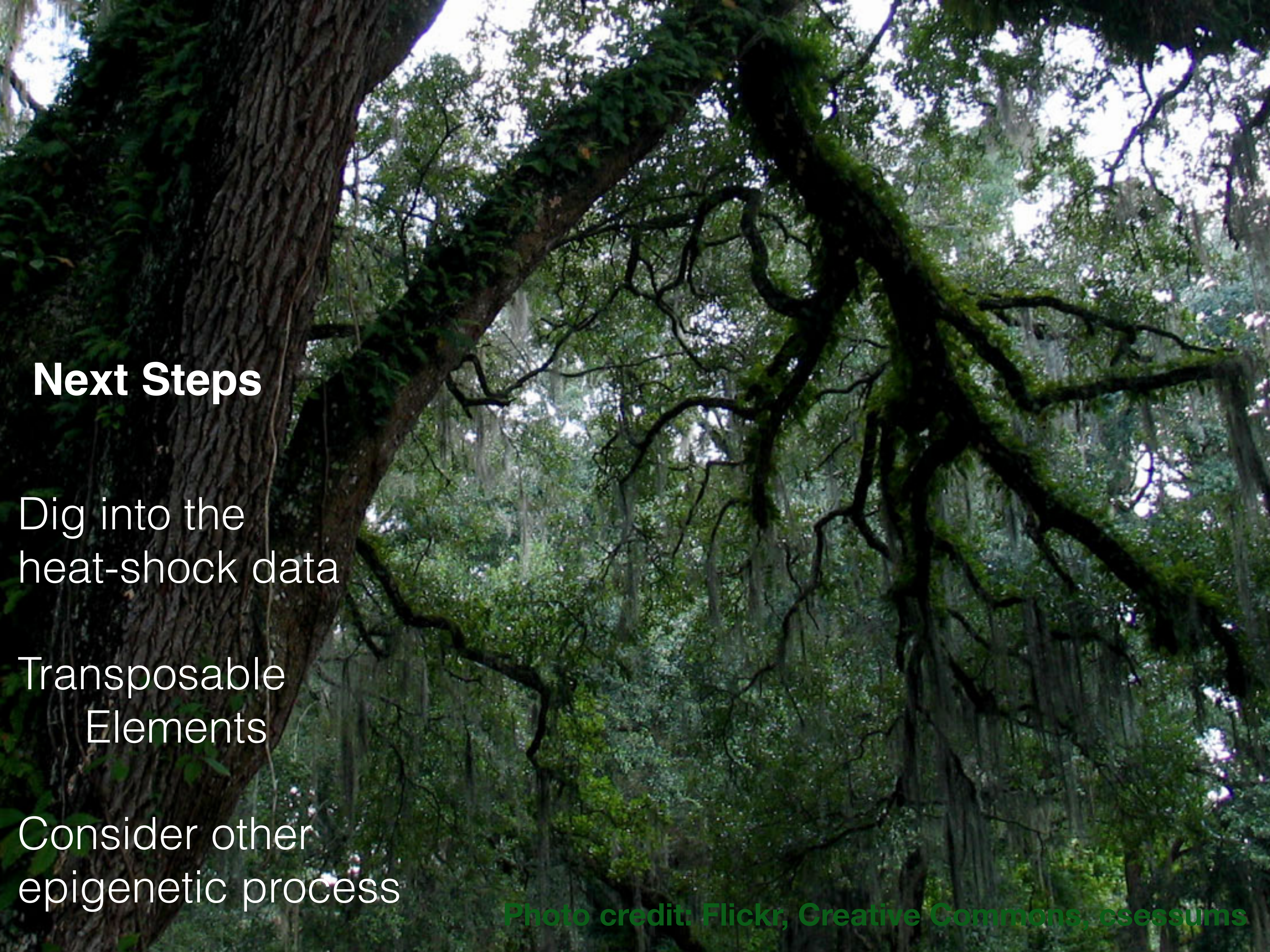


Photo credit: Flickr, Creative Commons, csessums

Next Steps

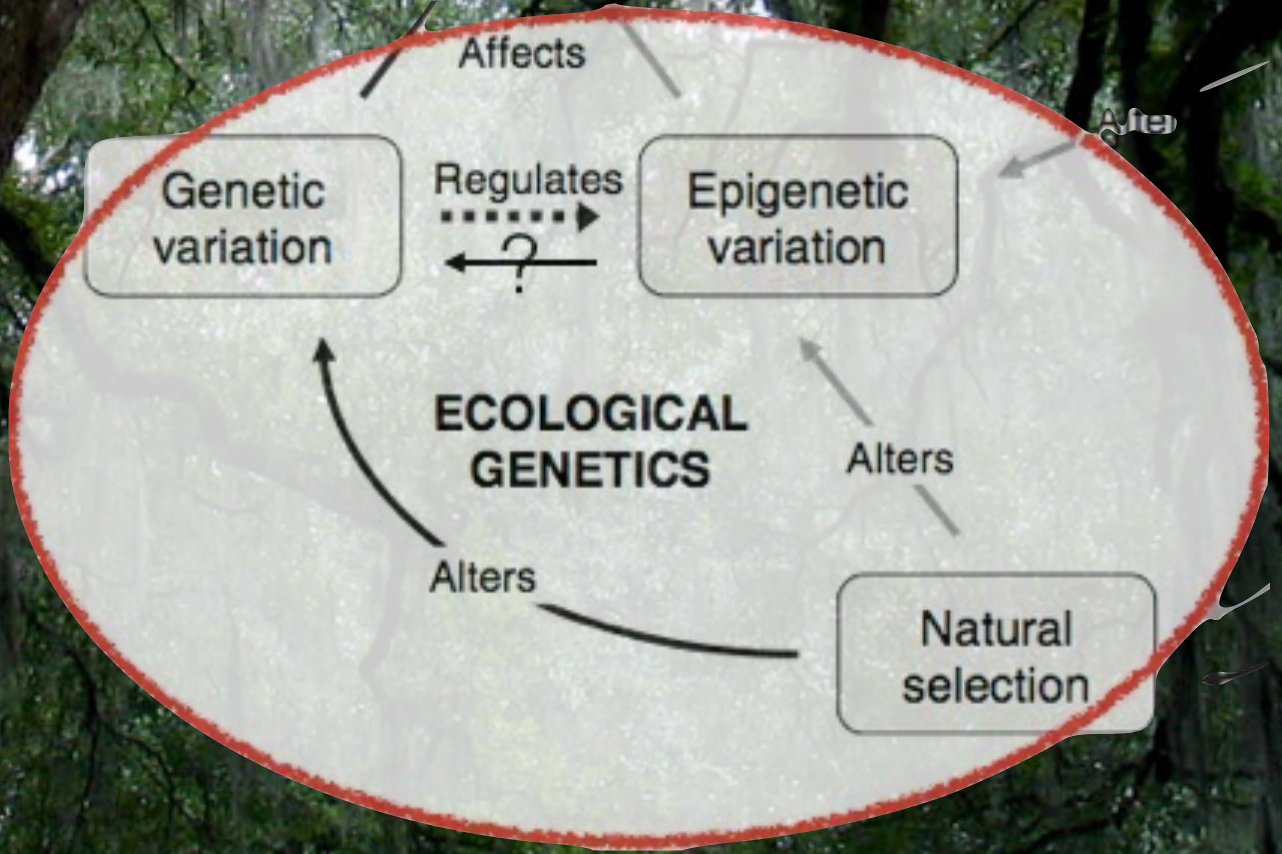


Photo credit: Flickr, Creative Commons, csessums

Very new ~~data~~

Heritability

Plasticity

Local Adaptation

Genetics

versus

Epigenetics

Common Garden Experiment

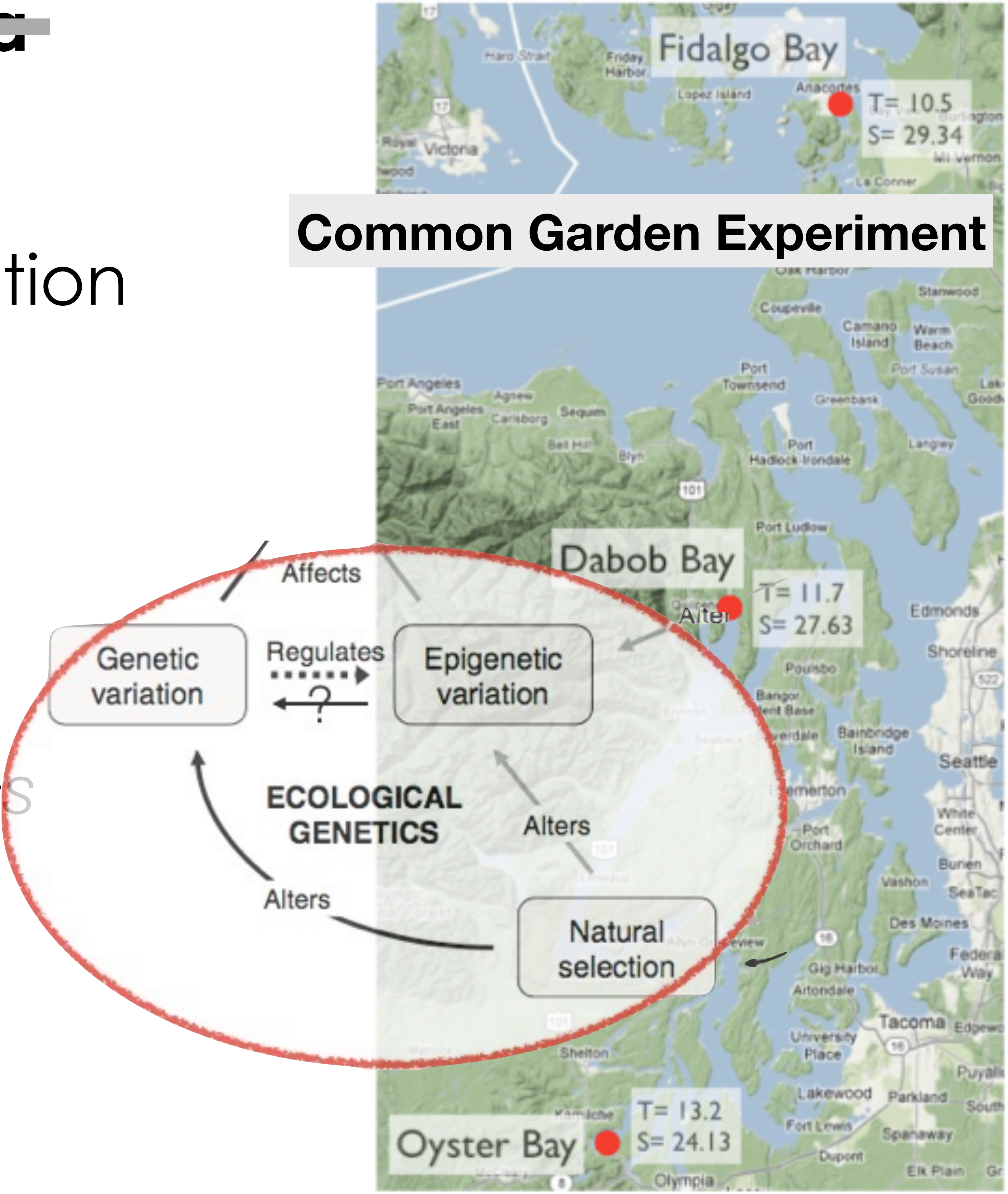
Very new ~~data~~

Heritability

Plasticity

Local Adaptation

Common Garden Experiment



Genetics
versus
Epigenetics

Acknowledgements

Mackenzie Gavery
Claire Olson
Sam White
Brent Vadopalas
Jake Heare
Jay Dimond

NSF

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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NOAA
U.S. DEPARTMENT OF COMMERCE

Bill Howe
Dan Halperin

eScience Institute

USDA

slides, data & more @ robertslab.info