Consequences of folate depletion during development for DNA methylation and gene expression in the fetal mouse

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BiGCaT bioinformatics

Developmental Origins of Health & Disease

e.g. Lillycrop *et al* 2005, BJN

e.g. Waterland & Jirtle, Mol & Cell Biol, 2003

e.g. Sinclair *et al* 2007, PNAS

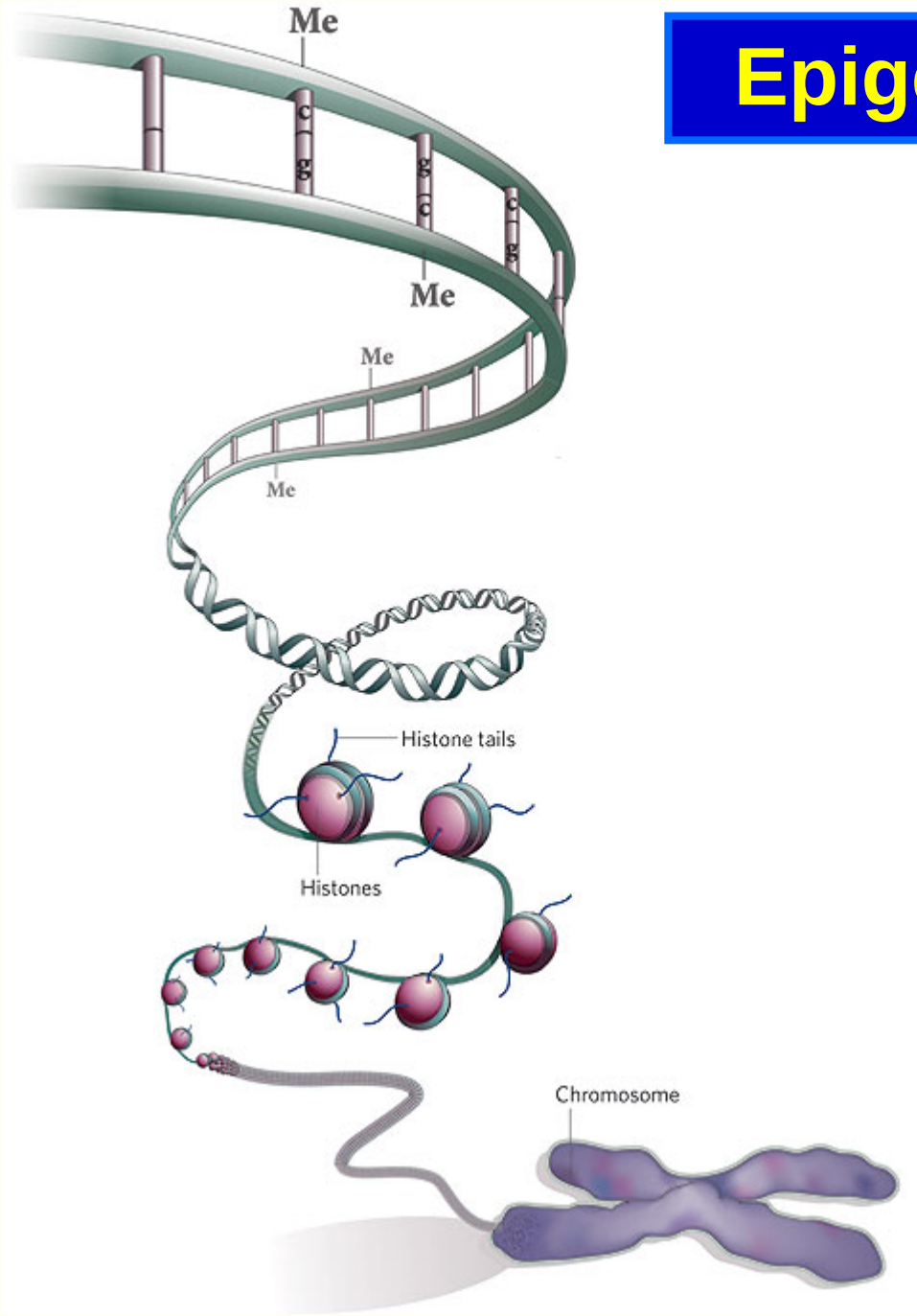
Nutritional Insults *in utero*

Altered Programming

Adulthood

Increased disease risk

Epigenetic Mechanisms



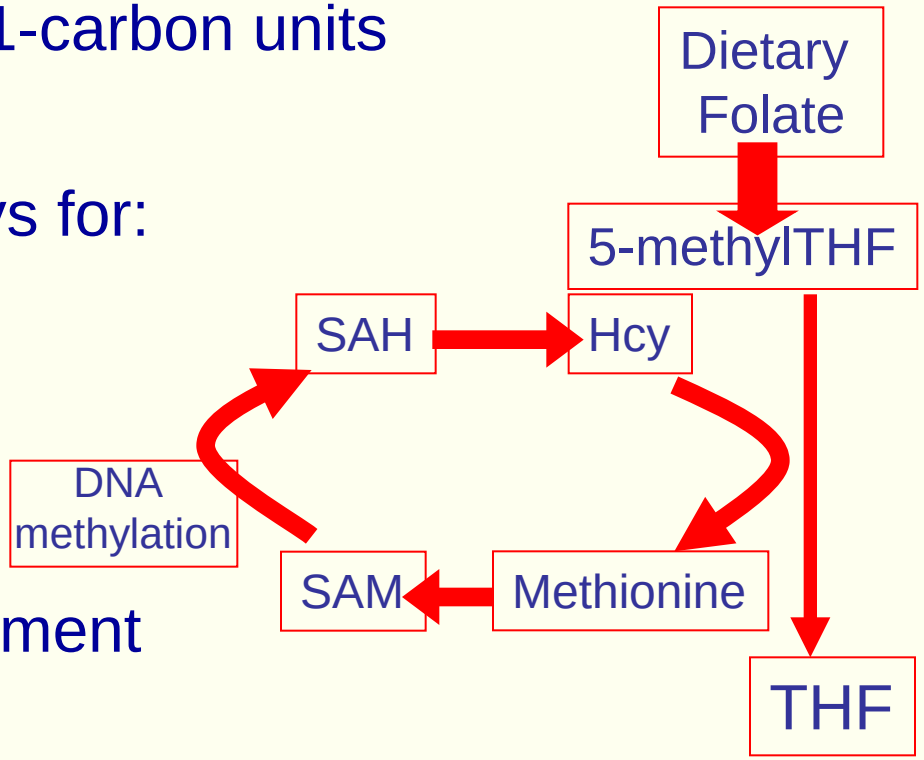
- Candidate mechanisms for developmental programming
- Established *in utero*
- Modifiable by environmental factors
- Influence gene expression

DNA methylation

Qiu J (2006) *Nature* **441**, 143-145

Folate

- Metabolic role in transfer of 1-carbon units
- Important in cellular pathways for:
  - amino acid interconversion
  - nucleic acid biosynthesis
  - methylation of biological molecules
- Essential for normal development
- Low folate intake during pregnancy is associated with increased risk of NTDs



Hypothesis

Offspring of folate depleted mothers have altered gene expression caused via DNA methylation changes

Folate Depleted Mouse Model

Mating
D0

Sampling
D17.5

2 weeks

4 weeks

Gestation

Control Diet

Lab Chow

Low Folate Diet

Hepatic RNA assessed for gene expression changes

Hepatic DNA methylation assessed

Control diet: 2 mg/kg Folic acid
Low folate diet: 0.4 mg/kg Folic acid

Gene Expression Arrays

Male Liver Tissue

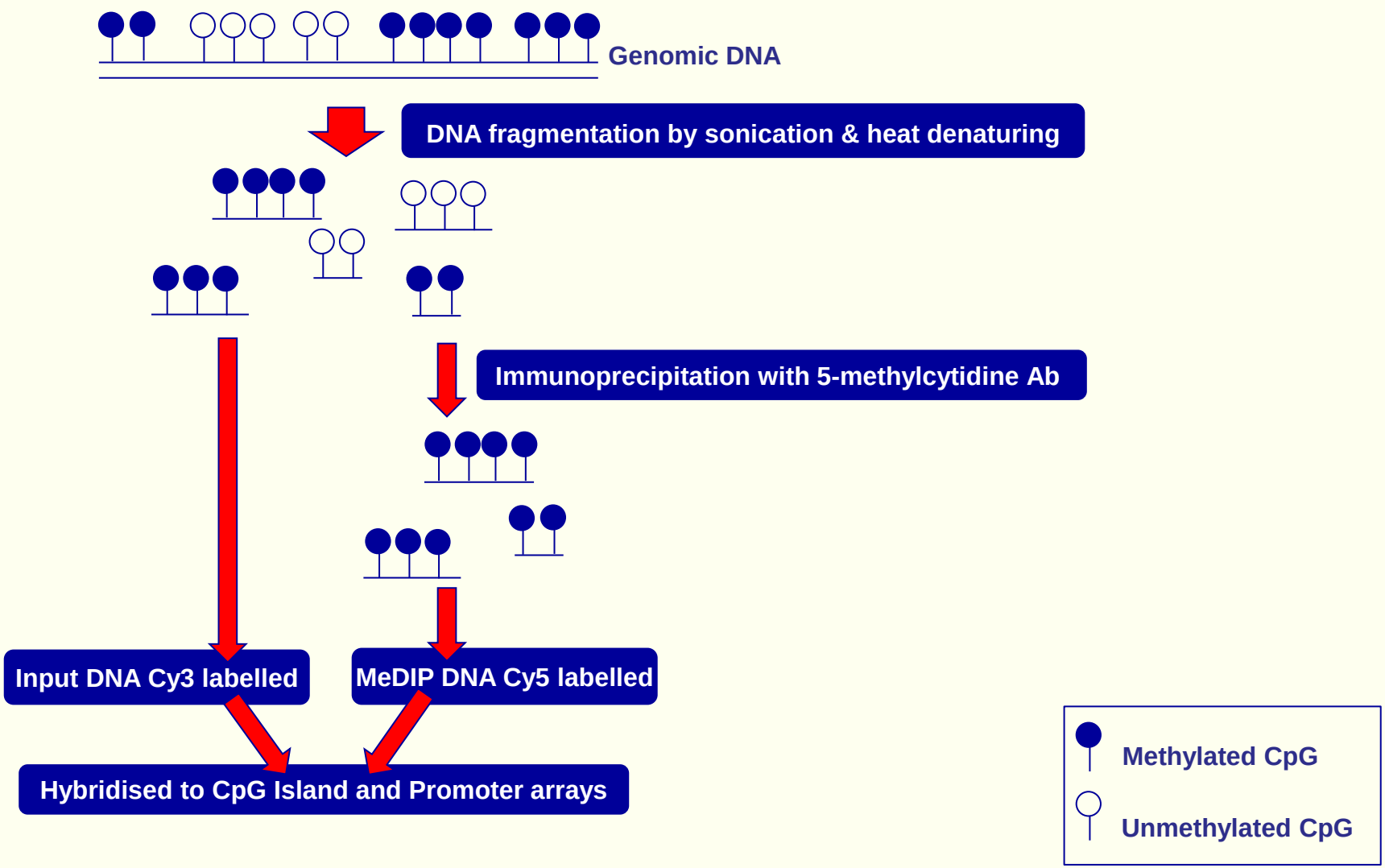
RNA & DNA extraction

RNA Quality check

Shipped to Service XS

Affymetrix whole genome mouse array
n = 6/group

Methylated DNA Immunoprecipitation (MeDIP) for Methylation Arrays



Array Analysis

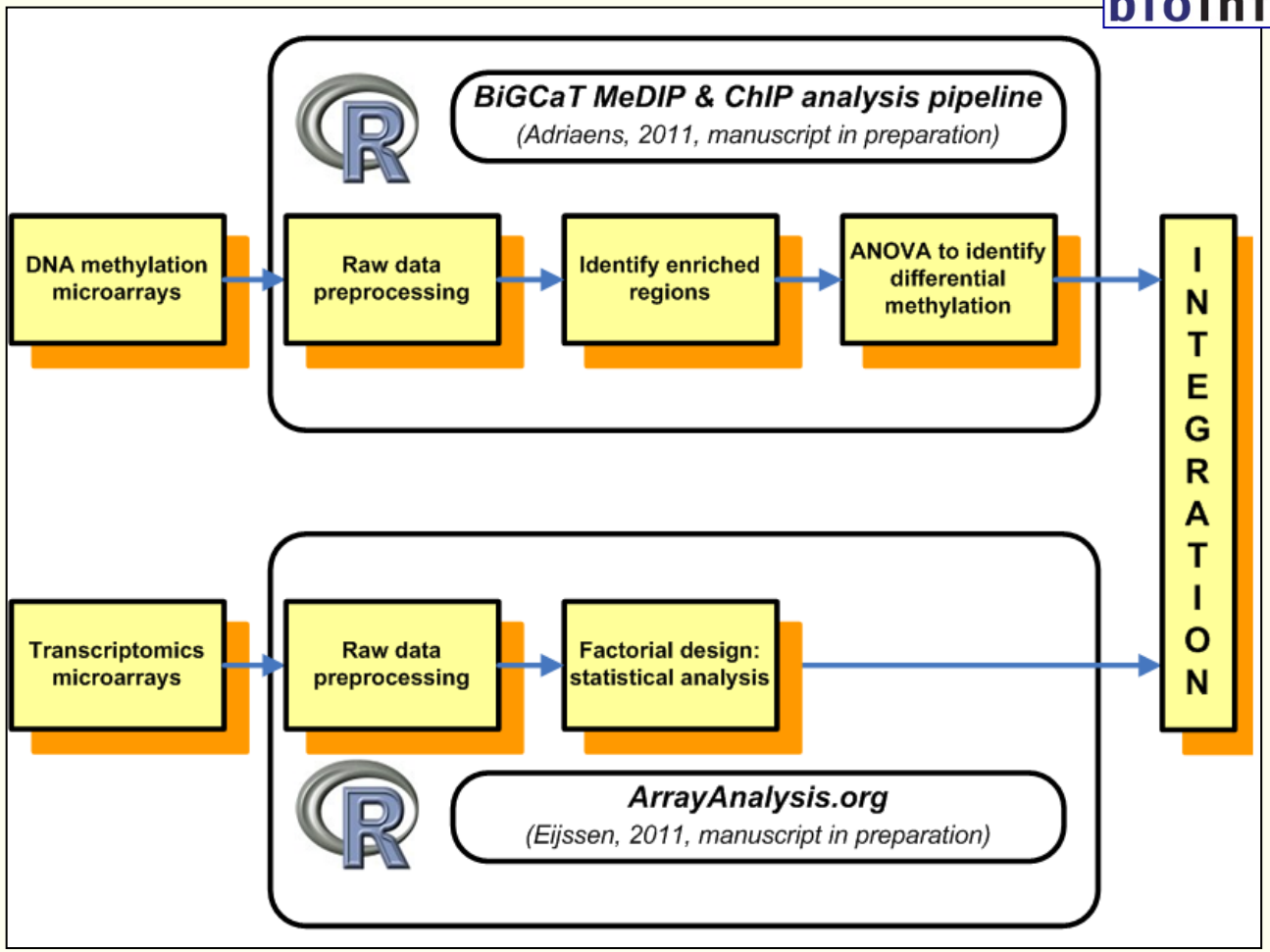
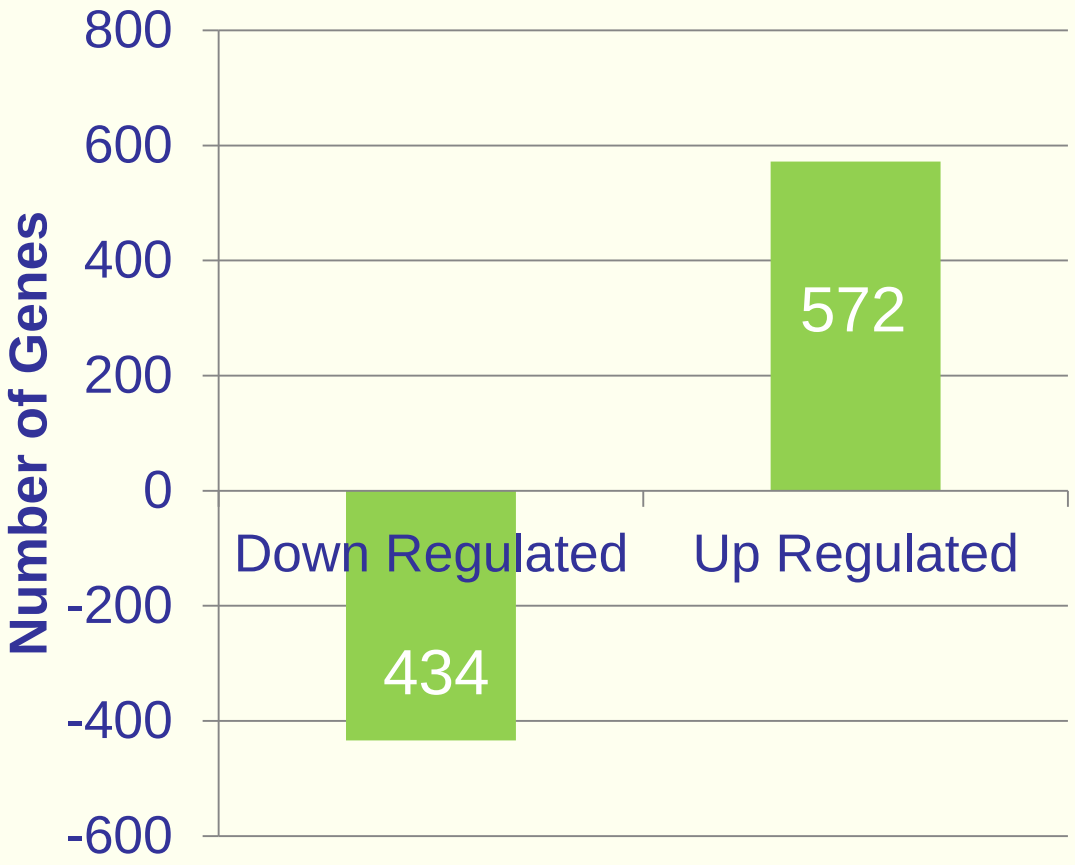


Figure composed by Michiel Adriaens

Poster: 'Consequences of folate depletion during development and high fat intake from weaning on adiposity, gene expression and DNA methylation in adult mice. "

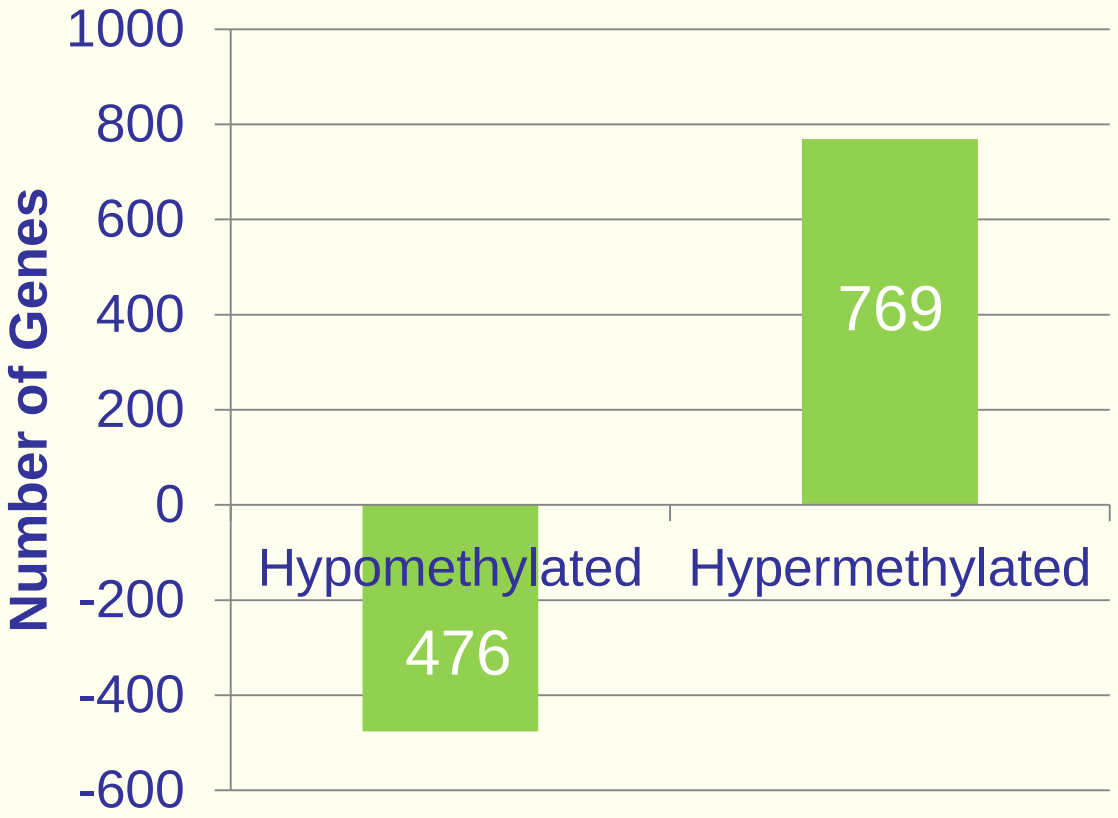
Gene expression changes in response to low maternal folate

- Fold change
  >1.2 or < -1.2
- Significant
  P value <0.05

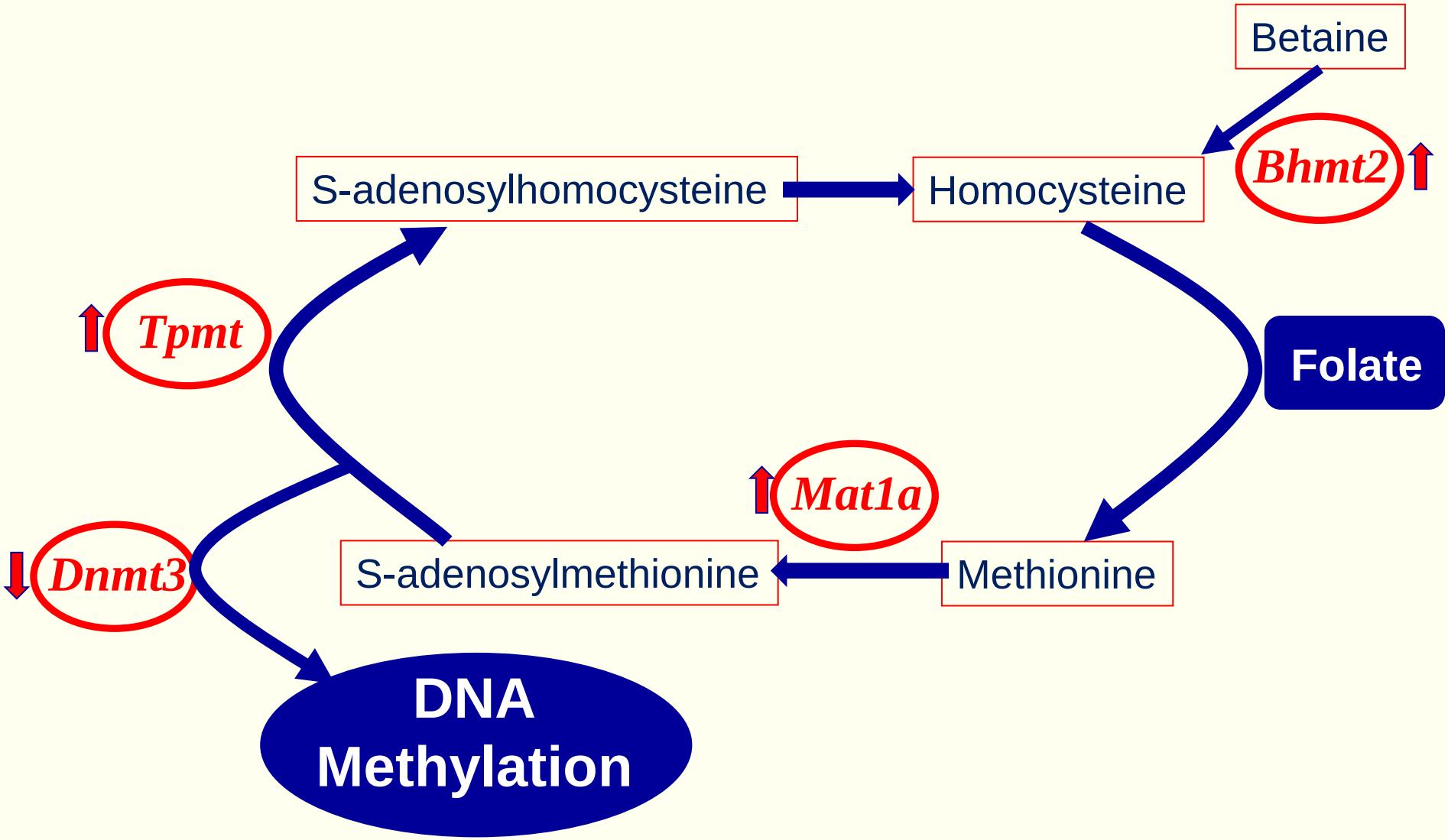


DNA methylation changes in response to low maternal folate

- Significant
  P value <0.05

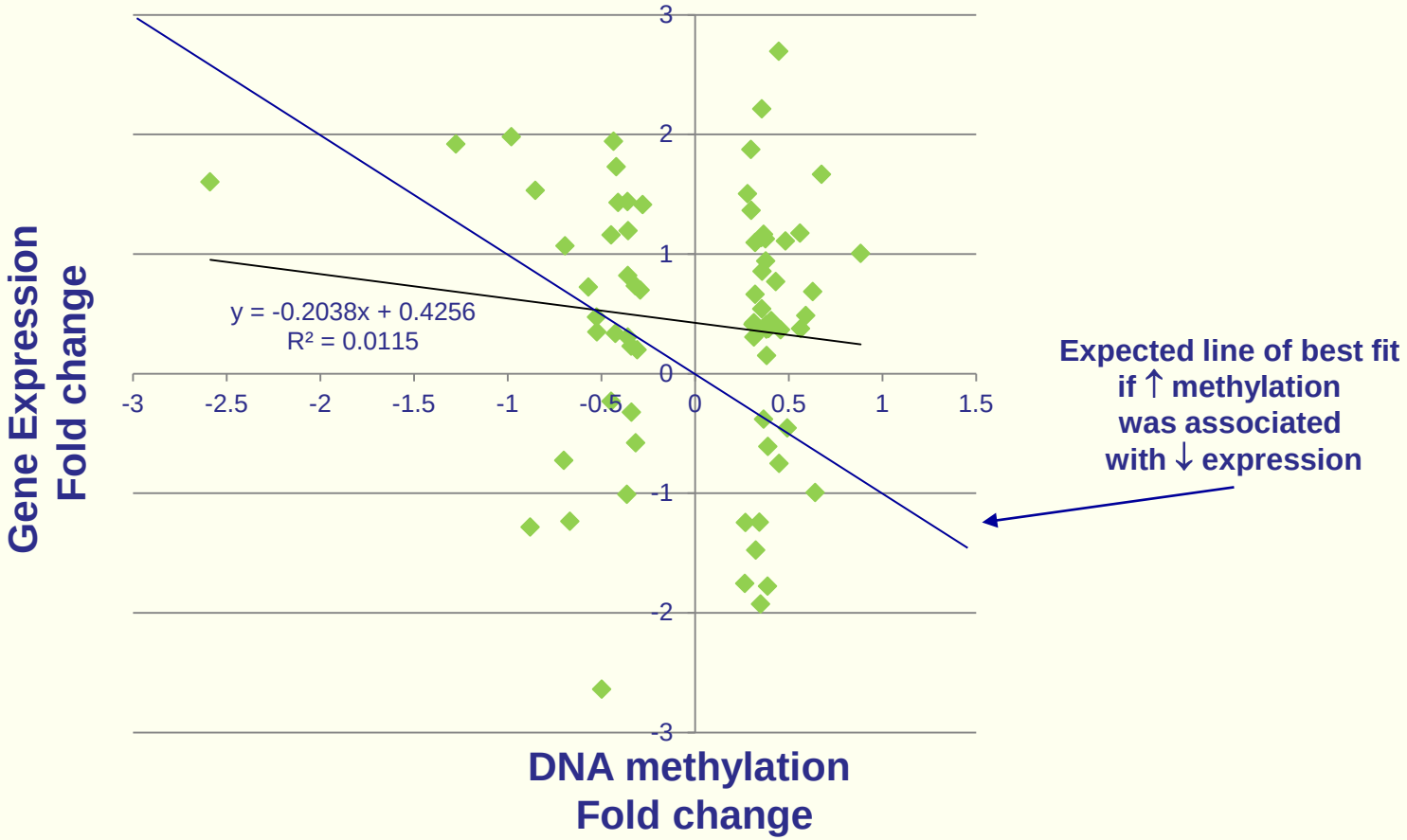


Possible Mechanism



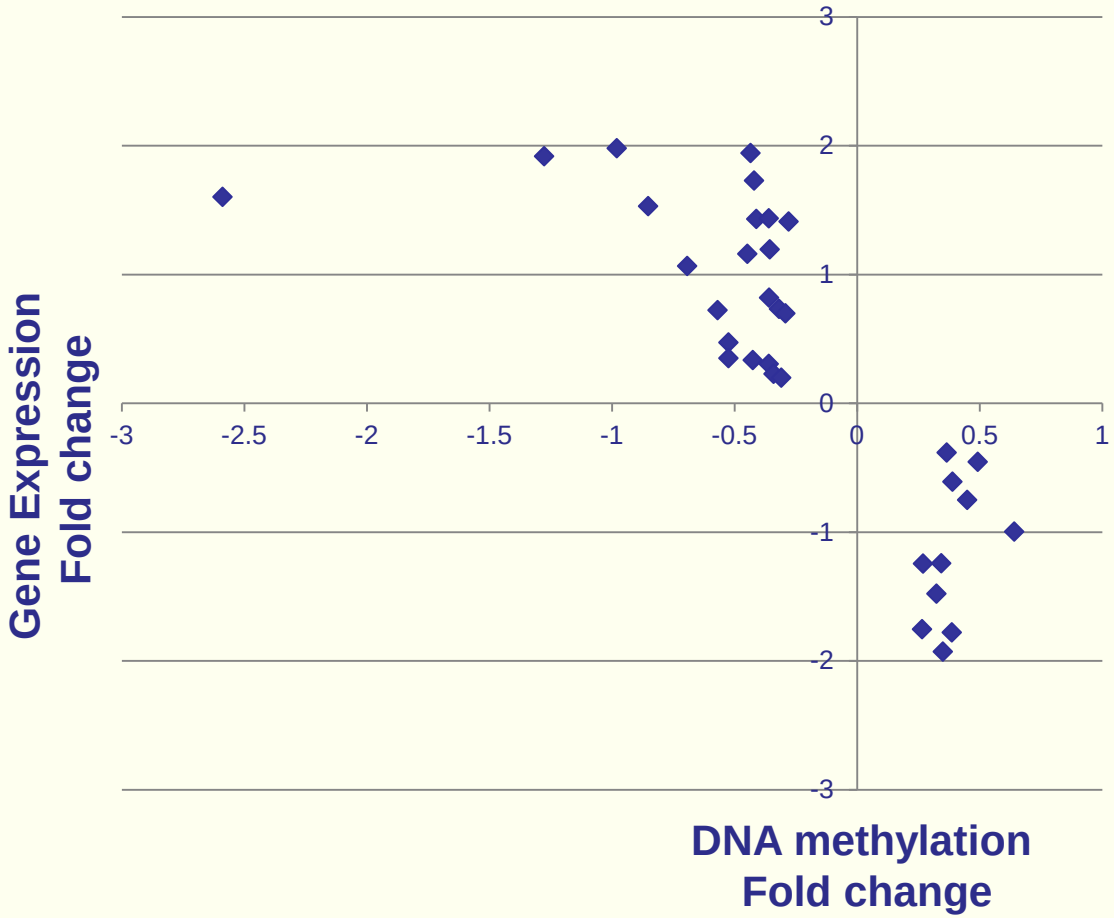
Genes with altered expression & DNA methylation

72 genes were differentially expressed AND differentially methylated in response to low maternal folate



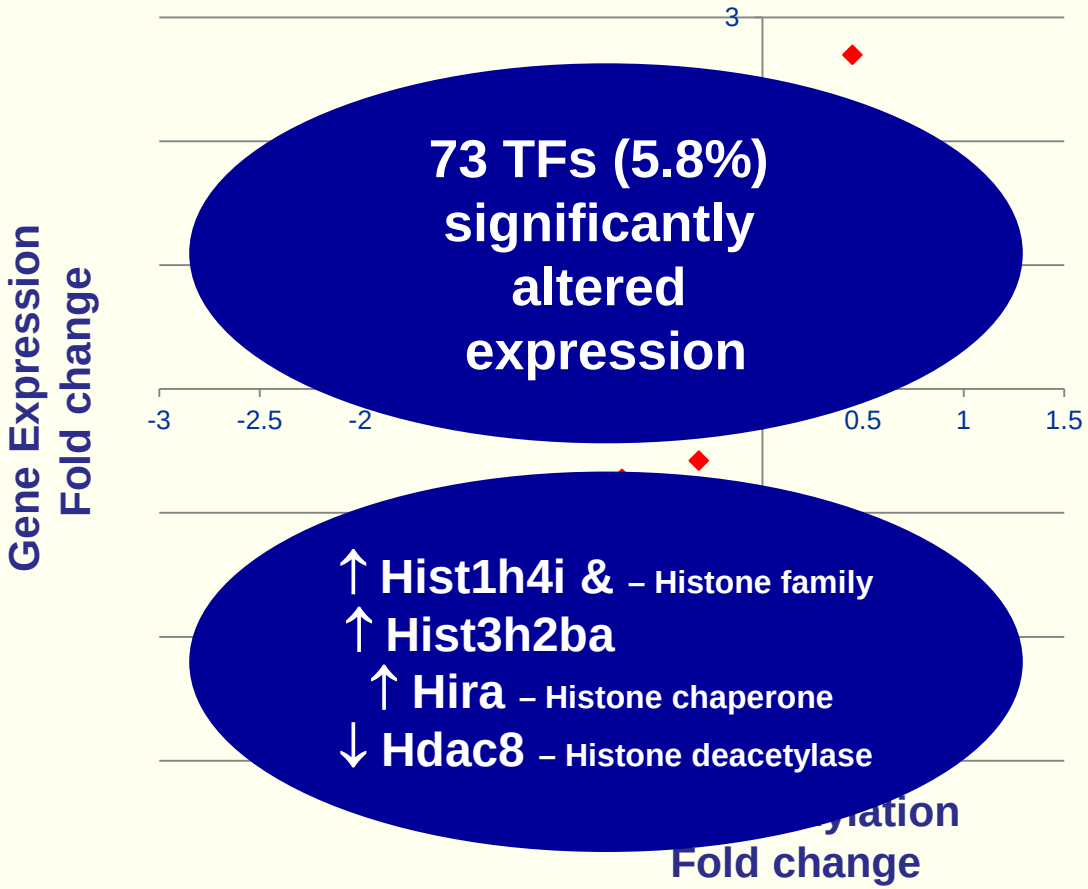
Direct Effects

Changes in gene expression of 33 genes were potentially caused by changes in DNA methylation:
DNA methylation ↑, gene transcription↓



Indirect Effects

Changes in gene expression of 39 genes were caused by other mechanisms: altered expression of transcription factors, histone modifications or post-transcription µRNA events



Conclusions

- Maternal low folate alters both gene expression & DNA methylation in fetal liver
- More genes were hypermethylated than hypomethylated in response to low folate
- 72 genes were differentially expressed AND methylated in response low maternal folate
- Suggests mechanisms other than DNA methylation are involved in observed altered gene expression e.g. changes in transcription factor expression, histone modifications etc
- It is essential to consider both direct and indirect effects when integrating epigenomic and transcriptomic data

Acknowledgments

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hnrc molecules to populations

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