Epigenome-wide Analyses

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Frame the Research Question

- What is your research question?

- Is epigenome-wide the best approach?
  - Candidate gene vs. exploratory analysis
  - Array vs. sequencing

- Know the strengths and weaknesses of your selected approach
  - Islands, shores, shelves
  - Promoters, TSS, Enhancers

Define Your Study Population

- Sample size

- Characteristics (Ethnicity, sex, etc.)

- Effect modification

  – Restrict? => generalizability

  – Stratify? => power

- Confounding

  – Matching => need to adjust for matching factors in analysis

Interpretation of Your Results

- No standard analyses **!**
- Adjust for multiple comparison
  - optimal FDR, number of tests, correlation between loci
- Functional relevance
  - Expression
  - Location
- Statistical significance
- Absolute difference in methylation
- Biologic relevance
  - Gene function

Interpretation of Your Results

- What does a difference in methylation in a single CpG mean?

- What does a statistically significant difference in methylation of 79.6% vs. 80.4% mean?

- What is hypomethylation? What is hypermethylation?

- Methylation does not always correlate with expression!

Periconceptional Folic Acid and IGF2 Methylation

	No Folic Acid (n = 34)	Yes Folic Acid (n = 86)	P-value
Complete DMR	0.474 (0.007)	0.495 (0.004)	0.014
CpG #1	0.473 (0.009)	0.484 (0.005)	0.292
CpG #2&3	0.334 (0.006)	0.348 (0.004)	0.059
CpG #4	0.590 (0.016)	0.632 (0.010)	0.023
CpG #5	0.511 (0.011)	0.516 (0.080)	0.602

Linear Mixed Model analysis. Independent absolute methylation of the CpG dinucleotides without adjustments is presented in mean and (standard error).
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Epigenome-wide Methylation Analyses

Have to validate results with bisulfite pyrosequencing!!