Environmental Epigenetics
A role in cardiovascular disease?
Epigenetics

• Programming of gene expression that:
  – does not depend on the DNA code
  – (relatively) stable, i.e., replicated through:
    • cell mitosis
    • meiosis, i.e. transgenerational (limited evidence in humans)

• Characteristics of epigenetic programming
  – Modifiable (can be reprogrammed)
  – Active or poised to be activated:
    • Potentially associated with current health states or predict future events
A musical example

DNA

Phenotype

Epigenetics
Epigenetics & Music Use the Same Markings

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Epigenetics & Music Use the Same Markings

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Epigenetic markings

DNA methylation
Methyl marks added to certain DNA bases **repress** gene transcription

Histone modifications
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These **alter** the activity of the DNA wrapped around them

microRNAs
Small non-coding RNAs that **block translation** of messenger RNAs into proteins
AIR POLLUTION
(Particulate Matter, PM)

- A ubiquitous threat
- Accounts for 3.2 million deaths/year
- A primary contributor to cardiovascular morbidity and mortality
  - acute effects (hours)
  - chronic effects (years)

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Concentrated Ambient Particle (CAP) exposure

Coarse CAP

Fine CAP
Effects of fine CAPs on blood pressure and DNA methylation

Bellavia et al. JAHA 2013

Effect on Blood Pressure

Effect on Blood DNA methylation

Differences of fine CAP exposure vs control
PM, heart rate variability (HRV) and TLR2 methylation

**Study Design**
Longitudinal Cohort: Normative Aging Study
573 elderly men, 1354 measures
2000-2011

**HRV Measurement**
 Measurement: 7-min ECG
Analysis:
1. Time-domain methods:
   - SDNN (standard deviation of NN intervals)
2. Frequency-domain methods:
   - HF (0.15-0.4 Hz, parasympathetic activity)
   - LF (0.04-0.15 Hz, sympathetic and parasympathetic)

**Air pollution and epigenetics**
PM$_{10}$ from time resolved geospatial satellite (AOD) based methods
TLR2 methylation measured on blood DNA
Individuals with higher TLR2 methylation have stronger HRV reductions upon PM exposure peaks (48 hrs windows)

Low TLR2 methylation group

High TLR2 methylation group

Zhong et al, JAHA 2014
Can diet (flavonoids) protect us from air pollution?

- **Conclusions**
  - Differential methylation in innate immunity genes may confer susceptibility to adverse cardiac autonomic effects of PM2.5 exposure in older individuals
  - Higher flavonoid intake may attenuate these effects, possibly by decreasing *TLR2* methylation.

Zhong et al, JAHA 2014
Could we finally have the “Cool Juice”?  

• In the 1990s’ sitcom “Family Matters”, America’s undisputed King of Nerds Steve Urkel (to the left) drank his “Cool Juice” and transformed himself in Stefan Urquelle (to the right)  
• Can a “cool juice” make our epigenome (and lives) healthier?
Challenges in (environmental) epigenetics

• Exposures
  – How do we measure them?

• Small effects
  – Exposures are widespread
  – Effects are usually expected to be small

• Sample size
  – Epigenetic studies often require large study populations
Using satellite data to reconstruct air pollution levels

http://modis.gsfc.nasa.gov/

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Satellite-derived air pollution (PM$_{2.5}$)

- every and each day since 2000
- any single address worldwide
- needs surface data for calibration
Challenges in (environmental) epigenetics

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Epigenetic haplotyping on the 450k Infinium BeadChip
Adjacent-site clustering (A-clustering)

- Most EWAS studies analyze each CpG methylation site independently
- While straightforward, this approach does not consider:
  - Correlation of methylation levels between adjacent sites
  - Co-regulation of sites within same functional region
- We developed **A-clustering** to detect sets of neighboring CpG sites that are correlated with each other
  - It uses an algorithm that creates CpG clusters based on correlations of adjacent CpG sites
  - Sites within regions identified by A-clustering are modeled as multivariate responses to environmental exposure

Sofer et al. Bioinformatics 2013
A-clustering results

- Clusters differ in size
- In an analysis of farmers exposed to pesticides:
  - Identified effects missed by the single CpG analysis
  - Low computing time
  - Robust to specifications

Sofer et al. Bioinformatics 2013
Challenges in (environmental) epigenetics

• Exposures
  – How do we measure them?

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CHARGE Consortium

http://web.chargeconsortium.com/
http://depts.washington.edu/chargeco/wiki/Main_Page
Leading role in GWAS meta-analyses

- 287 publications as of September 2014
- Several in high impact journals
  - 56 in Nature Genetics
  - 35 in PLOS Genetics
  - 23 in Hum Mol Genetics
  - 13 in Diabetes
  - 10 in Circulation
  - 7 in Nature
  - 3 in JAMA
  - 3 in Lancet
  - 3 in NEJM
  - 1 in PNAS
  - 1 in Science
**CHARGE cohorts with epigenome-wide methylation data**

### Caucasians

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### African Americans

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Summary, current questions, opportunities

• The epigenome is environmentally sensitive
  – Targeted by environmental exposures
  – Biomarkers reflecting exposures/risks
  – Potential mediator

• Challenges and possible answers
  – Challenges typical of environmental studies (exposure assessment, small effects, sample size)
  – Computational methods, consortia

• Ongoing/current research
  – Interventions
  – EWAS studies
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