A Systematic Review of Preterm Birth and DNA Methylation in African American women

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# Faculty Disclosure

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<thead>
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<tr>
<td>Conflicts of Interest</td>
<td>None</td>
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<td>Sponsorship/Commercial Support</td>
<td>None</td>
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Goals and Objectives

Session Goal:
◦ Describe findings of a systematic analysis of existing studies on DNA methylation and preterm birth among African American women

Session Objectives:
◦ Identify three limitations of existing studies on DNA methylation and preterm birth among African American women
◦ Discuss recommendations for future research in this area
Background

Preterm birth

- Definition
- Prevalence
- Significance
- Risk factors
Percent preterm births by race and Hispanic origin of mother, United States, final 2013 data

- All races: 11.38%
- NH White: 10.17%
- NH Black: 16.26%
- AI/AN: 13.04%
- Asian/PI: 10.14%
- Hispanic: 11.3%

NH=Non-Hispanic

Martin et al., National Vital Statistics Reports 2015
Risk factors

- Medical
- Obstetric
- Social
- Environmental
Epigenetic inquiry

- Shared maternal/fetal environment
- DNAm common biomarker for preterm birth
- Racial differences in DNAm may contribute to outcome
- Epigenomic paths of inquiry are relevant
DNA Methylation

How environment turns genes on or off

DNA - 4 nucleotides (C,G,A,T)

Addition of methyl groups to Cytosine on DNA signals genes to turn on or off

Important for healthy cell development, and can also lead to disease (hypermethylation and CA)
Figure 1. Contributors to preterm birth

- Social and environmental exposures
- Medical and obstetric risk factors

Factors:
- Genetic factors
- Epigenetic factors

Result: Preterm Birth
Methods

- Systematic review of Medline and CINAHL
- Inclusion criteria
- Search terms: DNA methylation, preterm birth, gestational age, preterm birth
Records identified via searches (n=279)

Records after duplicates removed (n=271)

Abstracts/full-text articles screened (n=271)

Records excluded (n=261)

Studies included in review (n=10)
Results

- N=10 studies reviewed
- All included African Americans
- Overall, DNAm was associated with preterm birth
<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Sample size</th>
<th>Preterm birth</th>
<th>Tissue source</th>
<th>Epityping</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Behnia, 2015</td>
<td>Nashville, TN</td>
<td>N=70 (13% AA)</td>
<td>22-36 weeks gestation (+ contractions/ cervical changes)</td>
<td>Placental fetal membranes (amniochorion)</td>
<td>Candidate gene/ targeted</td>
<td>Higher methylation status of CpG islands within the OXTR promotor in infants born preterm</td>
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<td></td>
<td>Nashville Biobank</td>
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<tr>
<td>Burris, 2012</td>
<td>Boston, MA</td>
<td>N=1160 (10% AA)</td>
<td>&lt;37 weeks gestation</td>
<td>Maternal and umbilical cord, DNAm</td>
<td>LINE-1</td>
<td>Preterm birth is associated with lower LINE-1 in cord blood</td>
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<td>Project Viva</td>
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<tr>
<td>Filiberto, 2011</td>
<td>Providence, RI</td>
<td>N=480 (10% AA)</td>
<td>SGA, LGA</td>
<td>Placenta</td>
<td>Candidate gene/ targeted</td>
<td>Significant relationship between differential (increased) methylation and large for gestational age</td>
</tr>
<tr>
<td>Lee, 2012</td>
<td>Baltimore, MD</td>
<td>N=141 (64% AA)</td>
<td>&lt;37 weeks</td>
<td>Umbilical cord blood</td>
<td>EWAS</td>
<td>Gradual changes in DNAm associated with gestational age</td>
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<td>Liu 2013</td>
<td>Durham, NC</td>
<td>N=73 (54%)</td>
<td>&lt;37 weeks</td>
<td>Umbilical cord blood</td>
<td>Candidate gene/targeted</td>
<td>No DNAm difference found between types of PTB</td>
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<tr>
<td>Michels 2011</td>
<td>Boston, MA Epigenetic Birth Cohort</td>
<td>N=319 dyads (12%)</td>
<td>&lt;37 weeks, term ≥37w</td>
<td>Umbilical cord blood/placenta</td>
<td>LINE-1</td>
<td>PTB associated with lower LINE-1 methylation compared to term</td>
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<tr>
<td>Parets 2013</td>
<td>Nashville, TN Nashville Biobank</td>
<td>PTB n=22, term n=28 (100%)</td>
<td>24-34 weeks, controls: &gt;39 weeks</td>
<td>Umbilical cord blood</td>
<td>Candidate gene/targeted</td>
<td>29 CpG sites associated with PTB</td>
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<tr>
<td>Parets 2015</td>
<td>Nashville, TN Nashville Biobank</td>
<td>PTB n=16, term n=24 (100%)</td>
<td>24-34 weeks, controls: &gt;39 weeks</td>
<td>Maternal leukocytes</td>
<td>EWAS</td>
<td>No CpG sites associated with PTB, but DNAm between maternal-fetal pairs correlated</td>
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<td>Schroeder 2011</td>
<td>Atlanta, GA, Nashville, TN</td>
<td>2 Cohorts: n=259 (10%), n=194 (57%)</td>
<td>&lt;37 weeks, LMP, OB estimate</td>
<td>Umbilical cord blood</td>
<td>Candidate gene/targeted</td>
<td>CpG sites on several genes associated with gestational age</td>
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<tr>
<td>Vidal 2013</td>
<td>North Carolina, NEST Cohort</td>
<td>N=397 (41%)</td>
<td>LBW, Preterm: &lt; 37 weeks</td>
<td>Umbilical cord blood</td>
<td>Candidate gene/targeted</td>
<td>Increased DNAm at PLAGL1 DMR associated with higher birthweight</td>
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Discussion

- Exposure measurement:
  ◦ Varying definitions of preterm birth
  ◦ PTB vs. Gestational Age

- Limited inclusion of AA’s

- Small sample sizes, no or small comparison groups

- Varying methodologies for methylation analysis
  ◦ GWAS vs. sites vs. regions
Limitations

- Race in epigenetic studies
- Three studies: same biobank
- Need for more research
Recommendations

- Standardized definitions/methodologies
- Tissue types
- Maternal or fetal focus?