Preliminary Examination of Racial Disparities in Cerebral Palsy:
Using gene expression and clinical data

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Racial Disparities in CP

• In a review of literature published since 1993, reports on CP prevalence show Black children have a higher prevalence than White children.
  – % Difference in prevalence ranged from 15-29%

• Most recently Maenner et al (2012) reported the CP prevalence for Black children to 3.9 per 1000 children.
  – Whites: 2.7/1000 children;
Racial Disparities in CP

• There is a striking lack of research focused on understanding the cause(s) of racial disparities in CP.

• Searching US-based studies published 1993, we found only 1 study which attempted to explain racial disparities in CP by investigating basic socio-demographic factors along with the onset of prenatal care, birthweight, and gestational age.
Low Birthweight and Preterm Birth

• Low birthweight and preterm birth are powerful predictors of CP.

• Hypothesized that Black-White difference in prevalence of low birthweight and preterm birth are the cause of the Black-White disparities in CP.

• However, Black-White disparities in CP prevalence have been found even among term and normal birthweight infants.
• Are there any other pathways that may lead to disparities?
Infection/Inflammation

• Research suggests that maternal infections during pregnancy increase the risk of having an infant being diagnosed with CP.

• Many maternal infections including chorioamnionitis disproportionately affect black women.

• Inflammatory responses to maternal infection mediated by cytokines and chemokines may not be the same for every racial or ethnic group.
Birth Asphyxia

• Black children have a higher risk of birth asphyxia than White children.
  – California study: Wu et al (2004) found Blacks were 28% more likely than Whites to be diagnosed with birth asphyxia.
  – National study: Mohamed et al (2014) found Black were 23% more likely than Whites to have a diagnosis of birth asphyxia.
Objective

- Describe socio-demographic, clinical, and biological factors occurring during pregnancy and in the immediate perinatal period that may lead to racial disparities in CP using gene expression and clinical data.
Data Source

• Data stem from the Origins, Wellness & Life-history in CP (OWL) Study
  – 2009-2012 matched case-control study
  – Children with and without CP
  – Born in Michigan
  – Age 2-15 years at time of recruitment
  – Specialty and Primary Care Clinics
    • Ann Arbor, Lansing, and Grand Rapids Michigan
Data Source

• Multiple sources of data in the OWL Study
  – Birth Certificate
  – Maternal & Child Hospital Discharge Abstracts
  – Maternal Interview
  – mRNA isolated from Archived Newborn Bloodspots
Prelim Racial Disparities Study

Participants restricted to:

- CP diagnosis
- Race: Black or White
  - child’s race was defined by maternal race.
- Birth Certificate and Microarray Data available
- White children had to have:
  - birth year ± 1 year of a Black child with CP
  - gestational age group similar to that of a Black child with CP
    - <28 wks, 28-32 weeks, >37 weeks
## Overall Sample Characteristics (N=89)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>84.5 (75)</td>
</tr>
<tr>
<td>Black</td>
<td>15.7 (14)</td>
</tr>
<tr>
<td><strong>Birth Year</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), Range</td>
<td>2003 (4), 1994-2009</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57.3 (51)</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), Range, &lt;37 weeks</td>
<td>35.6 (5.8), 23-42</td>
</tr>
<tr>
<td></td>
<td>31.5 (28)</td>
</tr>
</tbody>
</table>
Statistical Analysis: Clinical Data

In all clinical data analyses:

• Predictor variable: race
• Outcome: maternal or child characteristic of focus
• Categorical Characteristics
  – Used Logistic Regression with robust error estimation
  – Used Exact Logistic Regression when maximum likelihood estimation did not converge.
• Continuous Characteristics
  – Linear regression with robust error estimation
Statistical Analysis: Clinical Data

• Unadjusted and adjusted regression models
  – adjusted for child’s birth year, sex, and gestational age for all outcomes.

  – When examining disparities in functional limitations, regression models where further adjusted for CP type.
    • child’s birth year, sex, gestational age, and CP type

• Used a relaxed p-value of 0.10 to denote statistical significance.
Clinical Data Outcomes

• Socio-demographic (at time of child’s birth)
  – Maternal Age
  – Maternal Education
  – Medicaid Coverage

• Pregnancy & Birth Characteristics
  – Birthweight
  – Fetal Growth (Small- and Large-for-gestational age)
  – 5 minute Apgar Score
  – Labor & Delivery Complications
  – Signs of Neonatal Encephalopathy
  – Maternal Infection

• Cerebral Palsy
  – CP Type (hemiplegic, diplegic, quadraplegic)
  – Functional Limitations (gross motor, manual ability, and communication)
Statistical Analytic: Microarray Data

- 7 gene sets (3 empirical; 4 canonical) representing four physiological pathways hypothesized to contribute to the development of cerebral palsy.
  - Inflammatory*
  - Hypoxic*
  - Thyroidal
  - Coagulative
Statistical Analytic: Microarray Data

• Used Gene Sets Net Correlations Analysis (GSNCA) to assess differences in intergene correlations in gene sets between Black and White children with CP.
  – Differences between groups in the structure of genes’ cross-correlations for a given gene set.
  – Adjusted for birth year, sex, and gestational age.
RESULTS
RESULTS: CLINICAL DATA
Maternal Characteristics\textsuperscript{a,b}

\textsuperscript{†}Adjusted for birth year, sex, gestational age.

\begin{itemize}
  \item \textsuperscript{a} At time of child’s birth.
  \item \textsuperscript{b} N= 89 children (14 Black; 75 White)
\end{itemize}
Birth Characteristics

† Adjusted for birth year, sex, gestational age.

<table>
<thead>
<tr>
<th></th>
<th>% LBW</th>
<th>% SGA</th>
<th>% LGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>64.3</td>
<td>35.7</td>
<td>7.1</td>
</tr>
<tr>
<td>White</td>
<td>30.7</td>
<td>14.7</td>
<td>4.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted p-value</th>
<th>Adjusted† p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LBW</td>
<td>0.031</td>
<td>0.052</td>
</tr>
<tr>
<td>% SGA</td>
<td>0.121</td>
<td>0.044</td>
</tr>
<tr>
<td>% LGA</td>
<td>0.502</td>
<td>0.879</td>
</tr>
</tbody>
</table>

a. N= 89 children (14 Black; 75 White)
Birth Characteristics

† Adjusted for birth year, sex, gestational age.

Mean 5 min Apgar Score

<table>
<thead>
<tr>
<th>Mean 5 min Apgar</th>
<th>Unadjusted p-value</th>
<th>Adjusted† p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.644</td>
<td>0.509</td>
</tr>
</tbody>
</table>

N= 89 children (14 Black; 75 White)
Labor & Delivery Complications

† Adjusted for birth year, sex, gestational age.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted p-value</th>
<th>Adjusted† p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>1.0</td>
<td>0.950</td>
</tr>
<tr>
<td>Severe</td>
<td>0.497</td>
<td>0.382</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.504</td>
<td>0.760</td>
</tr>
<tr>
<td>Mild</td>
<td>0.713</td>
<td>0.894</td>
</tr>
</tbody>
</table>

*24 kid missing at least 1 source of clinical data. N= 65 (55 White and 10 Black)*
Signs of Neonatal Encephalopathy

† Adjusted for birth year, sex, gestational age.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted p-value</th>
<th>Adjusted† p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>0.100</td>
<td>0.394</td>
</tr>
<tr>
<td>Definite/Probable</td>
<td><strong>0.052</strong></td>
<td>0.230</td>
</tr>
<tr>
<td>Possible</td>
<td>0.185</td>
<td>0.920</td>
</tr>
</tbody>
</table>

24 kid missing at least 1 source of clinical data. N= 65 (55 White and 10 Black)
CP Type\textsuperscript{a}

† Adjusted for birth year, sex, gestational age.

a. 1 child missing information on CP type (n=88).
Severe Functional Limitations

† Adjusted for birth year, sex, gestational age, and CP type.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted p-value</th>
<th>Adjusted‡ p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Gross Motor(^b)</td>
<td>0.348</td>
<td>0.023</td>
</tr>
<tr>
<td>Severe Manual Ability(^c)</td>
<td>0.320</td>
<td>0.230</td>
</tr>
<tr>
<td>Severe Communication(^d)</td>
<td>0.102</td>
<td>0.095</td>
</tr>
</tbody>
</table>

a. 3 children missing information on functional scales (1 Black; 2 White). N=86
b. GMFCS LEVEL ≥ 4.
c. MACS LEVEL ≥ 4.
d. CFCS LEVEL ≥ 4.
RESULTS: MICROARRAY DATA
Hypothesized Pathways Leading to Cerebral Palsy

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene Sets, n=number of genes</th>
<th>GSNCA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulative</td>
<td>Canonical GO:0007596, (n=93)</td>
<td>0.1149</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Canonical GO:0050727, (n=31)</td>
<td>0.4305</td>
</tr>
<tr>
<td></td>
<td>Empirical FIRS, (n=36)</td>
<td><strong>0.0399</strong></td>
</tr>
<tr>
<td>Hypoxic/Asphyxial</td>
<td>Canonical ASPHYXIAL, (n=36)</td>
<td><strong>0.0420</strong></td>
</tr>
<tr>
<td></td>
<td>Empirical HYPOXIA.1, (n=31)</td>
<td>0.5184</td>
</tr>
<tr>
<td>Thyroidal</td>
<td>Canonical V$T3R_Q6, (n=199)</td>
<td>0.2797</td>
</tr>
<tr>
<td></td>
<td>Empirical T3.UP, (n=139)</td>
<td>0.0869</td>
</tr>
</tbody>
</table>
Discussion

• Preliminary results suggest low birthweight and fetal growth restriction may be one pathway through which racial disparities in CP manifest, but...

there may be more to the story.
Discussion

• In analysis of clinical data, we found no significant differences between Whites and Blacks in labor complications, signs of neonatal encephalopathy, maternal infection.

• However, significant differences in gene expression suggest asphyxia and inflammation may be physiological pathways through which racial disparities operate.

• Our preliminary results also a hormonal physiological pathways might also lead to racial disparities in CP.
Discussion

• Like Maenner et al (2012), we found Black children with CP were more likely to have severe gross motor function limitations than White children with CP.

• We also found Black children with CP had greater communication functional limitations communication than White children with CP.

• Additional research is needed to better understand what factors that drive these disparities in CP.
ACKNOWLEDGEMENTS

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  – Nigel Paneth, MD (PI)
  – Madeleine Lenski, MS
  – Qing Li, PhD

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References


References