A Novel Protocol for Characterizing Dysmorphology to Enhance the Phenotypic Classification of ASD in the Study to Explore Early Development

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The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.
Dysmorphology

- Dysmorphology is the description of physical features that are dysmorphic.
- A physical feature is defined as “dysmorphic” if it:
  - Has not followed the normal pattern of growth or formation.
  - Is often disproportionate when compared with a “typical” feature.
  - Occurs in ≤5% of the general population.
Examples of Dysmorphic Features
Dysmorphology Provides Clues to Cause

- Relatively flattened face
- Upslanting eyes
- Epicanthal folds
- Prominent tongue
- Small ears
- Redundant neck skin
- Wide spacing between the first and second toes
- Single transverse palmar creases
Why evaluate dysmorphology for children with ASD?

In children with ASD, the presence of multiple dysmorphic features might:

- Identify distinctive ASD phenotypes
- Serve as a potential marker for understanding cause and prognosis
Data Collection

- **Clinic Visit**--Exam and Dysmorphology Assessment
  - Performed by study staff familiarized with dysmorphology
  - Measurement of child height, weight, and head circumference
  - Measurement of child foot length
**Data Collection**

- **Clinic Visit**--Exam and Dysmorphology Assessment
  - Hand scans for measurements: Index finger length; Middle finger length; Ring finger length; Palm length; Total hand length
  - External exam for dysmorphic features: Head; Forehead; Hair; Face; Ears; Eyes; Eyebrows; Nose; Philtrum; Mouth; Lips; Teeth; Hands; Feet; Nails; Skin
Data Collection

- **Clinic Visit** -- Exam and Dysmorphology Assessment
  - Standardized photos of child
    - Obtain measurements: Interpupillary distance; Inner canthal distance; Palpebral fissure length; Philtrum length; Ear length
    - Document dysmorphic features
Seven clinical geneticists were each assigned a body region for which they performed a standardized dysmorphology review on all children in the study.

<table>
<thead>
<tr>
<th>Geneticist</th>
<th>Body Region</th>
<th># Features Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Art Aylsworth</td>
<td>Head, Hair, Face, &amp; Neck</td>
<td>68</td>
</tr>
<tr>
<td>Ellen Elias</td>
<td>Hands &amp; Feet</td>
<td>83</td>
</tr>
<tr>
<td>Julie Hoover-Fong</td>
<td>Growth &amp; Skin</td>
<td>16</td>
</tr>
<tr>
<td>Stuart Shapira</td>
<td>Ears</td>
<td>90</td>
</tr>
<tr>
<td>Stuart Shapira</td>
<td>Mouth, Lips, &amp; Teeth</td>
<td>26</td>
</tr>
<tr>
<td>Anne Tsai; Naomi Meeks</td>
<td>Nose &amp; Philtrum</td>
<td>52</td>
</tr>
<tr>
<td>Elaine Zackai</td>
<td>Eyes &amp; Eyebrows</td>
<td>62</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>TOTAL</strong></td>
<td><strong>397</strong></td>
</tr>
</tbody>
</table>
When is a Physical Feature Dysmorphic?

- **Occurs in ≤5% of the POP controls**
  - Absent vs. Present (e.g. Ear tag)
  - Spectrum in the Population (e.g. Ptosis)
    Statistical method applied to the POP group to categorize what part of the spectrum corresponds to “dysmorphic”

Absent Present

Absent

Mild

Moderate

Severe
The number of features considered dysmorphic for each child in POP were summed, Dysmorphology Scores were developed, and Scores fit to the log normal distribution.

Dysmorphology Classification

- ≤90% = Non-dysmorphic
- >90% and ≤95% = Equivocal
- >95% = Dysmorphic
### Study Population

<table>
<thead>
<tr>
<th>Child Race/Ethnicity</th>
<th>POP</th>
<th>ASD</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>186</td>
<td>317</td>
<td>503</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>98</td>
<td>119</td>
<td>217</td>
</tr>
<tr>
<td>Hispanic</td>
<td>91</td>
<td>90</td>
<td>181</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>375</td>
<td>526</td>
<td>901</td>
</tr>
</tbody>
</table>

- Dysmorphology reviews and classifications performed separately for each race/ethnicity
## Final Dysmorphology Classification

<table>
<thead>
<tr>
<th></th>
<th>POP</th>
<th></th>
<th>ASD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-dysmorphic</td>
<td>Equivocal</td>
<td>Non-dysmorphic</td>
<td>Equivocal</td>
</tr>
<tr>
<td><strong>NHW</strong></td>
<td>89.73%</td>
<td>7.03%</td>
<td>69.03%</td>
<td>13.87%</td>
</tr>
<tr>
<td><strong>NHB</strong></td>
<td>89.58%</td>
<td>4.17%</td>
<td>69.23%</td>
<td>13.68%</td>
</tr>
<tr>
<td><strong>Hisp</strong></td>
<td>90.00%</td>
<td>4.44%</td>
<td>73.56%</td>
<td>9.20%</td>
</tr>
</tbody>
</table>

χ²=2.72; p=0.606

χ²=1.40; p=0.844
Final Dysmorphology Classification

- Significant difference in the dysmorphology classification distributions between POP and ASD
  
<table>
<thead>
<tr>
<th>Total</th>
<th>Non-dysmorphic</th>
<th>Equivocal</th>
<th>Dysmorphic</th>
</tr>
</thead>
<tbody>
<tr>
<td>POP</td>
<td>89.76%</td>
<td>5.66%</td>
<td>4.58%</td>
</tr>
<tr>
<td>ASD</td>
<td>69.84%</td>
<td>13.04%</td>
<td>17.12%</td>
</tr>
</tbody>
</table>

  \[ \chi^2 = 51.26; \ p < 0.001 \]

- Partly attenuated by excluding those with known genetic syndromes

<table>
<thead>
<tr>
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<th>Non-dysmorphic</th>
<th>Equivocal</th>
<th>Dysmorphic</th>
</tr>
</thead>
<tbody>
<tr>
<td>POP</td>
<td>89.97%</td>
<td>5.57%</td>
<td>4.46%</td>
</tr>
<tr>
<td>ASD</td>
<td>72.52%</td>
<td>13.22%</td>
<td>14.26%</td>
</tr>
</tbody>
</table>

  \[ \chi^2 = 39.59; \ p < 0.001 \]
Summary

- This novel protocol defines a quantitative dysmorphology classification and identifies categories of Dysmorphic and Non-dysmorphic children with ASD in SEED.

- This classification allows stratification of ASD phenotype for potentially more homogeneous assessment categories for studies of etiologic risk factors and genetic susceptibilities.
Future studies have been initiated that focus on identifying patterns of dysmorphic features that are predictive of various ASD phenotypes.
Collaborators

- Aimee A. Alexander, CDC
- Arthur S. Aylsworth, UNC Medical School
- Ellen R. Elias, University of Colorado School of Medicine
- Julie E. Hoover-Fong, Johns Hopkins University
- Naomi J. L. Meeks, University of Colorado School of Medicine
- Laura A. Schieve, CDC
- Margaret C. Souders, Children’s Hospital of Philadelphia
- Ann C. H. Tsai, University of Colorado School of Medicine
- Marshalyn H. Yeargin-Allsopp, CDC
- Elaine H. Zackai, Children’s Hospital of Philadelphia

The participating families and the many staff and scientists from the SEED sites who contributed to the dysmorphology study
Highlights of the Findings of 5 SEED Studies

- **ASD Risk Factors Studies**
  - *Autism Spectrum Disorder and Birth Spacing* – Laura Schieve, PhD
  - *Maternal Infection and Fever during Pregnancy and Risk of ASD* – presented by M. Danielle Fallin, PhD on behalf of Lisa Croen, PhD

- **ASD Genetic Associations**
  - *Peripheral Blood DNA Methylation and ASD* – M. Danielle Fallin, PhD

- **ASD and Child Health Effects**
  - *Gastrointestinal Symptoms in 2 – 5 Year Old Children* – Ann Reynolds, MD

- **Characteristics of Children with ASD**
  - *A Novel Protocol for Characterizing Dysmorphismology to Enhance the Phenotypic Classification of ASD* – Stuart Shapira, MD, PhD
It's QUESTION TIME!!