

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

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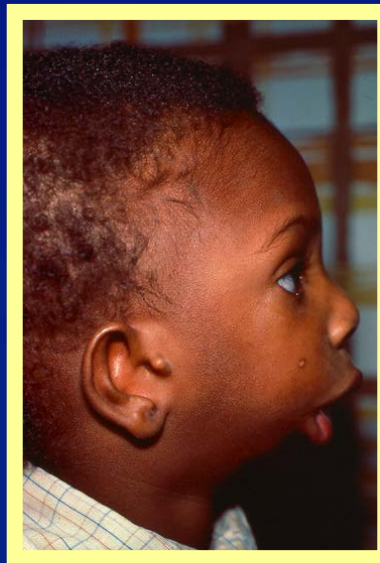
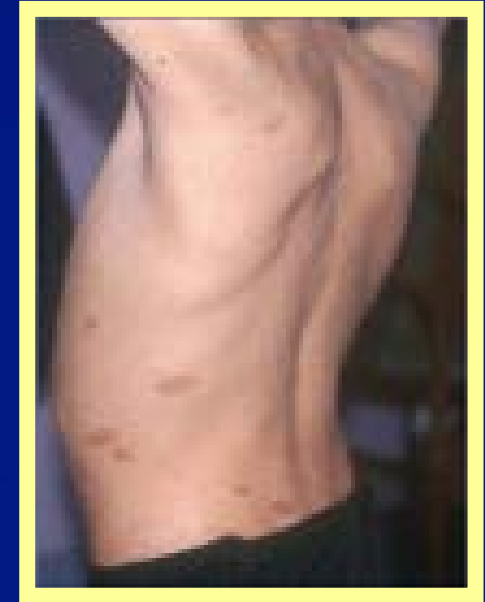
**Chief Medical Officer and Associate Director for Science  
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*The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency 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  $\leq 5\%$  of the general population**

## Examples of Dysmorphic Features



# Dysmorphology Provides Clues to Cause

Relatively flattened face

Upslanting eyes

Epicanthal folds

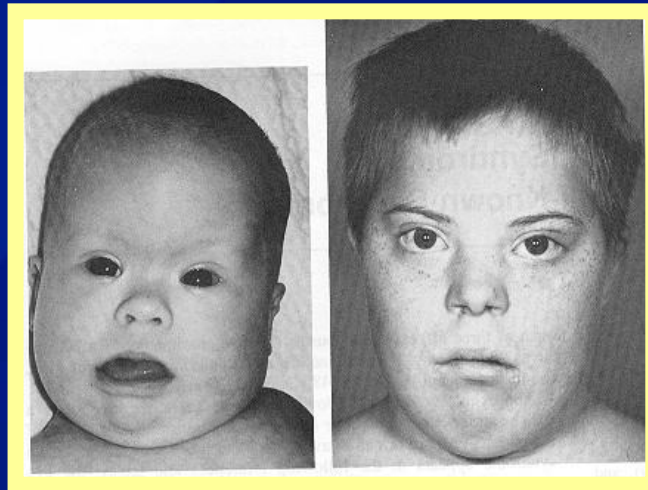
Prominent tongue

Small ears

Redundant neck skin

Wide spacing between the first and second toes

Single transverse palmar creases



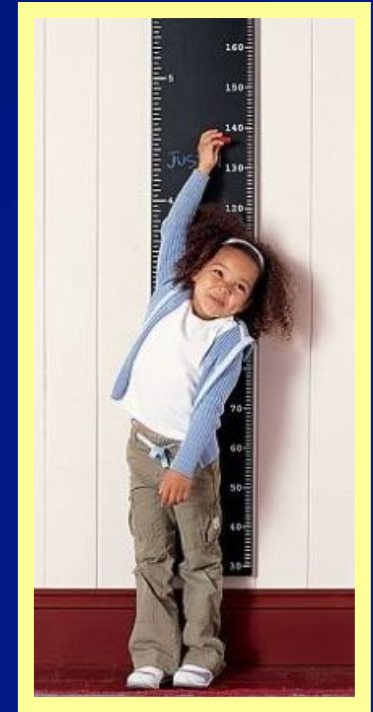
## **ASD and Dysmorphology**

- ❑ **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

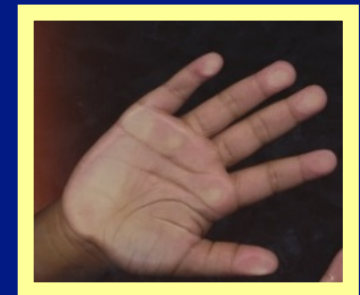
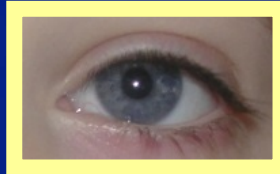
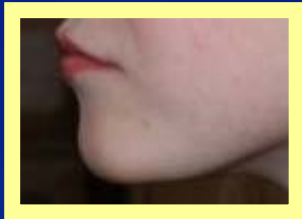
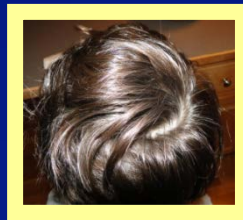
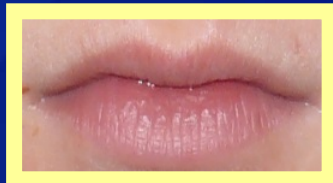
- Performed by study staff familiarized with dysmorphology
- Measurement of child height, weight, and head circumference
- Measurement of child foot length



# Data Collection

## □ Clinic Visit--Exam and Dysmorphology Assessment

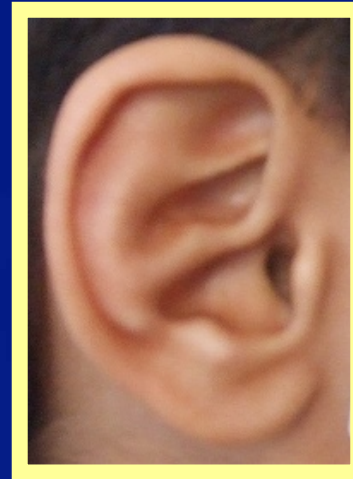
- Hand scans for measurements: Index finger length; Middle finger length; Ring finger length; Palm length; Total hand length
- External exam for dysmorphic features: Head; Forehead; Hair; Face; Ears; Eyes; Eyebrows; Nose; Philtrum; Mouth; Lips; Teeth; Hands; Feet; Nails; Skin



# 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





## Dysmorphology Review

- Seven clinical geneticists were each assigned a body region for which they performed a standardized dysmorphology review on all children in the study

Geneticist	Body Region	# Features Reviewed
Art Aylsworth	Head, Hair, Face, & Neck	68
Ellen Elias	Hands & Feet	83
Julie Hoover-Fong	Growth & Skin	16
Stuart Shapira	Ears	90
Stuart Shapira	Mouth, Lips, & Teeth	26
Anne Tsai; Naomi Meeks	Nose & Philtrum	52
Elaine Zackai	Eyes & Eyebrows	62
	<b>TOTAL</b>	<b>397</b>

# When is a Physical Feature Dysmorphic?

## □ Occurs in $\leq 5\%$ 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



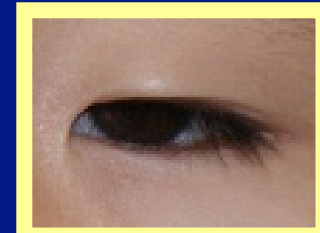
Absent



Mild



Moderate



Severe

# Dysmorphology Classification

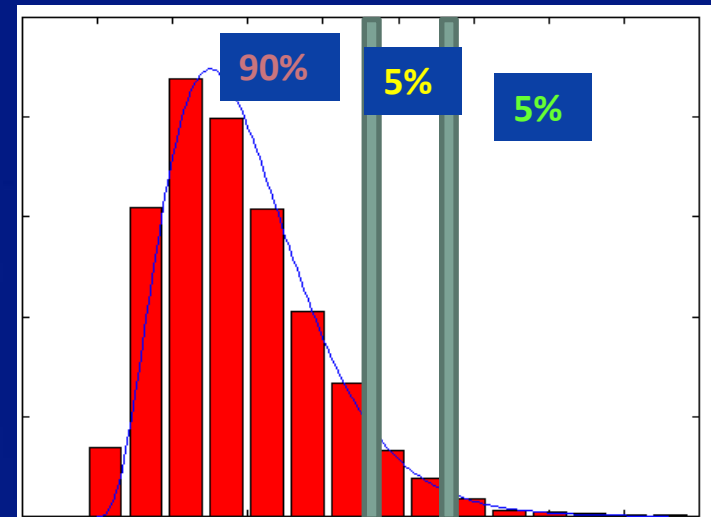
- The number of features considered dysmorphic for each child in POP were summed, Dysmorphology Scores were developed, and Scores fit to the log normal distribution

## Dysmorphology Classification

$\leq 90\%$  = Non-dysmorphic

$>90\%$  and  $\leq 95\%$  = Equivocal

$>95\%$  = Dysmorphic



## Study Population

Child Race/Ethnicity	POP	ASD	TOTAL
Non-Hispanic White	186	317	503
Non-Hispanic Black	98	119	217
Hispanic	91	90	181
TOTAL	375	526	901

- ❑ Dismorphology reviews and classifications performed separately for each race/ethnicity

## Final Dysmorphology Classification

POP			
	Non-dysmorphic	Equivocal	Dysmorphic
NHW	89.73%	7.03%	3.24%
NHB	89.58%	4.17%	6.25%
Hispanic	90.00%	4.44%	5.56%

$\chi^2=2.72$ ;  $p=0.606$

ASD			
	Non-dysmorphic	Equivocal	Dysmorphic
NHB	69.03%	13.87%	17.10%
NHW	69.23%	13.68%	17.09%
Hispanic	73.56%	9.20%	17.24%

$\chi^2=1.40$ ;  $p=0.844$

## Final Dysmorphology Classification

- ❑ Significant difference in the dysmorphology classification distributions between POP and ASD

Total	Non-dysmorphic	Equivocal	Dysmorphic
POP	89.76%	5.66%	4.58%
ASD	69.84%	13.04%	17.12%

$\chi^2=51.26; p<0.001$

- ❑ Partly attenuated by excluding those with known genetic syndromes

Total	Non-dysmorphic	Equivocal	Dysmorphic
POP	89.97%	5.57%	4.46%
ASD	72.52%	13.22%	14.26%

$\chi^2=39.59; p<0.001$

## 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**

## Summary

- ❑ **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

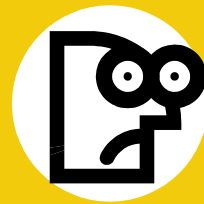
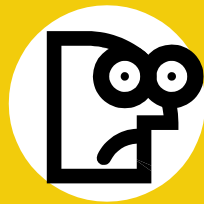
*Peripheral Blood DNA Methylation and ASD* – M. Danielle Fallin, PhD

- 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 Dysmorphology to Enhance the Phenotypic Classification of ASD* – Stuart Shapira, MD, PhD



**It's QUESTION TIME!!**