A Case Against Perfection
What is wrong with designing children, bionic athletes and genetic engineering?

Luis F. Escobar, MD
Medical Genetics & Neurodevelopmental Center

Genetic Breakthroughs

“Nobody’s perfect, but we’re working on it.”

Scientists are hoping to isolate a big hand gene to give people the power of flight.
Twenty-four ways to have children
Dr. David D. Weaver and Dr. Luis F. Escobar
American Journal of Medical Genetics

Moral Quandary
Cure Disease
Enhance physical or cognitive capacities

The primitive CNS
Neural Development

Brain-Spinal cord

4TH Week – Ventricular system

Diencephalon/Telencephalon
Ventricular Formation

Forebrain/Midbrain/Hindbrain

Human Embryo at Three months

Sulci and Gyri Development
13 weeks

26 weeks

35 weeks

Sulci & Gyri Development

Neurulation of the Human Embryo

Neurons:
Three developmental stages

- Cell Production
- Cell Migration
- Cell Differentiation

The Neuron
Parts of a Typical Neuron

Corticobulbar pathway

Golgi/Nissl Staining Method

- Dentritic spines on pyramidal neurons of the cerebral cortex

Corticospinal Tracts
Causes of Brain Malformations

**Exogenous:**
- nutritional, radiologic, viral,
- chemical, medications, or
- ischemic.

**Endogenous:** causes are genetic.

The Head

Microcephaly (AR)
Holoprosencephaly

Liscencephaly

Encephalocele

Macrogyria
Microgyria

Heterotopias

Schizencephaly

Fetal Brain Disruption Sequence
Cranial Arteries at term

Peri-ventricular Leukomalacia

Corticospinal Tracts

Understanding Autism: A genetics perspective

Luis F. Escobar, MD
Medical Genetics & Neurodevelopmental Pediatrics Center
Autism Spectrum Disorder

• Set of poorly understood neurodevelopmental disorders that are clinically heterogeneous with a spectrum severity

• Repetitive self-stimulatory behaviors and communication and socialization deficits

AJHG 82:7-9, 2008

The New Autism Spectrum Disorder (NASD) in the DSM-5: Autism Minus Intellectual Disability

| Less severe ASD | Clear impairments in social communication. Meets all diagnostic criteria including symptom severity greater than threshold. | Occasional rituals, repetitive behaviors and fixated interests; some interference.
|----------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Subclinical ASD Symptoms | Has some symptoms from one or both domains but no significant interference or impairment. | Odd mannerisms, some excessive preoccupations but docile, may have ritualized behaviors but do not interfere with daily activities.
| Normal Variation | Socially isolated or "awkward" | Some ritualized behaviors and preoccupations, but these are normal for developmental stage and cause no interference.

What Causes Autism

• As you explore the question of "what causes autism," you are likely to come across many individuals who are absolutely certain they know the answer. It's important to know, though, that the subject is highly controversial.
Autism & Brain Activity Patterns
Dorothy Bishop, Oxford University
November 2010

Functional magnetic resonance imaging (fMRI) scanners:
1. Sixty two children between ages 4 and 17
2. Reduce activity in specific brain areas
3. Absence of additional genetic or environmental factors

Autism: A Neurobehavioral Pattern

Brain Injury
Hypoxic – Ischemic Injury
Postnatal Exposure
Prenatal Environmental Exposures
Genetics Causes
Syndromes (single gene defects)
Copy # Variants
Metabolic Disorders
Malformations/Deformations


Luis F. Escobar, Meadow Heiman, Deborah Spoerner, Lynne Steffus, Lori Harter

Medical Genetics & Developmental Pediatrics, St. Vincent Children's Hospital of Indianapolis
JJ – 3 year old
- Autism
- Macrocephaly
- Delayed Milestones
- Cynodactyly

RR, 4 year old
- Macrocephaly
- Autism
- Delayed speech
- Delayed milestones

ZF, 6 year old

GD, 15 month old
- PDD
- Father PDD
- Hemophilia
- Macrocephaly
LB, 5 year old

- Macrocephaly
- Delayed milestones
- Clynodactyly
- Autism

Family A

Autism - Macrocephaly

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deutsch CK</td>
<td>63 patients</td>
<td>Macrocephaly linked to autistic children with poor verbal skills</td>
</tr>
<tr>
<td>Fidler DJ</td>
<td>41 patients and 133 first degree relatives</td>
<td>Macrocephaly in 12% of autistic children and 15% in relatives</td>
</tr>
<tr>
<td>Cole and Hughes</td>
<td>6 children: obesity, distinctive facial anomalies, MR, and Macrocephaly</td>
<td>New syndrome</td>
</tr>
<tr>
<td>Stevenson RE; et al</td>
<td>14% of autistic patients showed macrocephaly</td>
<td>Macrocephaly does not define a homogeneous subgroup of autistic children by clinical findings</td>
</tr>
</tbody>
</table>
Autism/Macrocephaly (AM)
Autism/Normocephaly (AN)

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>A/M, N=13</th>
<th>A/N, N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clynodactyly of 5th finger</td>
<td>76.92 (10)</td>
<td>7.69 (1)</td>
</tr>
<tr>
<td>Prominent forehead</td>
<td>69.23 (9)</td>
<td>7.69 (1)</td>
</tr>
<tr>
<td>Midface hypoplasia</td>
<td>61.53 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Smooth philtrum</td>
<td>38.46 (5)</td>
<td>-</td>
</tr>
<tr>
<td>Scapular asymmetry</td>
<td>38.46 (5)</td>
<td>7.69 (1)</td>
</tr>
<tr>
<td>Displacement of occipital whorl</td>
<td>23.07 (3)</td>
<td>7.69 (1)</td>
</tr>
</tbody>
</table>

Observations

- Autism-Macrocephaly represents a subset of patients with unique clinical features on physical exam and behavioral patterns
- Autism-Macrocephaly may represent a variable expression of the same disorder or a disorder with heterogeneous origin
- Recognition of these individuals is essential, to aid future studies in search for etiologic factors, and treatment modalities of autism

Autism-Macrocephaly

- Stevenson et al. (1997) had found progressive postnatal macrocephaly in 24% of 100 patients with autism and that 62% of such cases had a family history of macrocephaly
- Naqvi et al (2000) suggested that this may represent a recognizable syndrome within the autism behavioral phenotype

Low Density Lipoprotein Receptor-Related Protein 1B (LRP1B) Gene Anomalies: Role in neurodevelopment and induction of Autism Spectrum Disorder symptoms

Luis F. Escobar, MD., Megan Tucker, CGC, Dima El-Khechen, CGC.

Medical Genetics & Neurodevelopmental Center, Peyton Manning Children’s at St. Vincent Hospital and Health Services. Indianapolis, In 46260
1. 8 year old patient referred for evaluation of possible ASD
2. Neurobehavioral testing suggested the diagnosis of Autism
3. Born at term by SVD after an uncomplicated pregnancy with a BW of 7 lbs 8 oz.
4. Past medical history was unremarkable
5. Interstitial duplication of 634 Kb at 2q22.1
6. The duplicated area encoded for one single gene: LRP1B

**Case Report**

**Physical Phenotype:**
- Macrocephaly
- Hypertelorism
- Micrognathia
- Cleft palate
- Café au lait spots
- Axillary freckling

**Neuro-Behavioral Phenotype:**
- Autism Spectrum Disorder
- Obsessive Compulsive Behavior
- ADHD

**Gene Expression of LPR1B**

**LRP1B Gene Function**
- Endocytic trafficking of amyloid precursors
- Regulates neuronal migration early in gestation
- Accumulation of APP occurs in the neural cell surface inducing neurotoxic effects may occur if gene function is de-regulated
LPR1B Gene

- We suggest that the 2q22.1 duplication seen in our case is responsible for functional abnormalities of the LRP1B gene which caused the mild physical phenotype findings and neurobehavioral difficulties seen such as the Autism Spectrum Disorder features.

- Additional Family with same duplication: Dr. Rosemarie Smith (Maine Medical Partners Pediatric Specialty Care) in which the proband presents neurophenotypic findings compatible with Autism Spectrum Disorder.

Gene Interaction

- One Important Gene
- Multiple Genes—Enough to Meet Threshold
- Non-Autism Genes Contribute to Overload
- One or Several Autism Genes
- Environmental Triggers
- Gene Sequencing Disruptions

Combination

Activation of Backup Genes

Autism Avoided or Ameliorated

Autism Manifested

Gene Interaction

Gene Testing Examples
- PTEN
- MECP2
- CDKL5
- DHCR7
- RAI1
- COH1
- Others
Genomic Sites and Autism

Purple: Sites that have been linked to autism
Red and Yellow parallel chromosomes: copy number variants
Dark and light green: candidate genes

Deletion 17q12

17q12 Deletion Neurodevelopmental Disorders
Autism Study (N=382)

- Standardized evaluation of functional level
- Full family history and pedigree analysis
- Full dysmorphologic evaluation
- Molecular and Cytogenetic testing
- Biochemical – Metabolic screening

Genetic Autism Findings

<table>
<thead>
<tr>
<th>Condition/diagnosis</th>
<th>%</th>
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<tbody>
<tr>
<td>Confirmed Molecular Change</td>
<td>53</td>
</tr>
<tr>
<td>+ Biochemical – Metabolic markers</td>
<td>25</td>
</tr>
<tr>
<td>Syndromic Diagnosis</td>
<td>21</td>
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</tbody>
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Observations:

- By using a systematic diagnostic approach we have been able to improve the diagnostic rate from 3-9 % in the literature to 24 %.
- The diagnosis of idiopathic (90-95%) Autism is quickly changing as we are able to elucidate the heterogeneity of Autism.
- All children in this study were referred to our center not because of the suspicion of dysmorphology but because of the diagnosis of suspected diagnosis of autism.
- Would treatment change depending on the etiology of Autism? Further studies are needed.

Recurrent CNV in ASD

<table>
<thead>
<tr>
<th>Region</th>
<th>CNV</th>
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<tbody>
<tr>
<td>1q21.1</td>
<td>Del</td>
</tr>
<tr>
<td>3q29</td>
<td>Del</td>
</tr>
<tr>
<td>15q13.3</td>
<td>Del</td>
</tr>
<tr>
<td>16p11.2</td>
<td>Dup</td>
</tr>
<tr>
<td>16p13.11</td>
<td>Dup</td>
</tr>
<tr>
<td>17q12</td>
<td>Del</td>
</tr>
<tr>
<td>22q11.2</td>
<td>Del</td>
</tr>
</tbody>
</table>
Autism Spectrum Disorder
- Making the diagnosis of ASD
- Recognizing the etiology of ASD
- Developing a plan of care

Thank You