Genetics of Autism: From Chromosomes to Mitochondria

Dmitriy Niyazov, M.D.
Section Head – Medical Genetics
Ochsner Clinic Foundation, New Orleans, LA
Disclosures

I am on the Speaker Bureau of GeneDx, Combimatrix Diagnostics and America Compounding Center
Autism – is it genetic?

- If one twin meets a **strict** definition of autism:
  - 70% of identical and 5% of fraternal twins would have autism

- If one twin meets a **broad** definition of autism (ASD):
  - 90% of identical and 10% of fraternal twins would have autism

- Genetic & Environmental components
MYTH:  
- Autism is a causative diagnosis

FACT:  
- Autism is a description of symptoms and signs (descriptive diagnosis)  
- Autism as a part of a particular genetic defect (causative diagnosis)
Benefits of a true diagnosis

Preventive role:
Various organs may be affected and can be treated before any complications occur.

Recurrence risk estimate:
Empowers parents in their decision to have another child or prenatal diagnosis.

Treatment
Testing

- Chromosomal Microarray (SNP array)
- Fragile X
- Metabolic
- Mitochondrial DNA
- Whole Exome/Genome Sequencing
Genetic causes of Autism

- Chromosomal ~ 20-25%
- Fragile X ~ 3%
- Single genes ~ 15-20%
- Mitochondrial/Metabolic ~ 20-25%
- All ~ 60-70%
- 21 year-old-female
- Autism/ID
- Congenital deafness
- Deaf brother
- **Karyotype/FraX** – normal

**Chromosome 1p21 duplication**
De novo (30 genes)
Autism locus

**Chromosome 13q12 deletion**
Paternal (*GJB6*)
Hearing loss gene (recessive)

**Chromosome 13q12 mutation**
Maternal (*GJB2* gene del35G)
Hearing loss gene (recessive)

**Digenic hearing loss**
Autosomal recessive
Chromosomal

13-year-old female
CHD
Dysmorphic features
Essentially averbal
Autism
Severe ID
**Karyotype** – trisomy 21

**Microarray:**
Chromosome 15q11.2 deletion
Maternal
Single Gene Disorder

- Autism
- Developmental delay
- Facial gestault
- Macrocephaly
- Overgrowth

Sotos syndrome

NSD1 gene deletion
Fragile X

- **Most common cause of inherited ID in males**
- 1/2500-4000 males, 1/5000-8000 females
- **Autism** – up to 50%
- IQ 20-60 (normal is >70), speech delay
- FMR1 gene testing – 99% sensitive
Mitochondria & Autism

- Solid evidence indicating disturbance of mito energy metabolism in some autistic patients

- 7% to 64% of autistic children have mito dysfunction

- Regression, waxing/waning energy levels, easy fatigability, or multiple organs affected unexplained by other etiology

- Developmental regression and autism after vaccination in a 19-month old girl (Hannah Poling) who was found to have mito complex I & III deficiency
Mitochondria & Autism


- 112 children with autism and mito
- Delay (51%), Regression (52%), Seizures (41%), GI (74%), female (39%), high lactate (78%), pyruvate (45%)
- Much higher in autism & mito compared with general autism population

*JAMA* 304:2389-96 (2010)

- Patients aged 2 to 5 years (364 autism, 289 control)
- Oxphos capacity, mtDNA mutations, lactate/pyruvate
- Children with autism were more likely to have mitochondrial dysfunction, mtDNA overreplication, and mtDNA deletions than typically developing children
**MYTH:**
- All mitochondrial diseases are severe

**FACT:**
- There is a very wide clinical variability with onset from conception to adulthood, asymptomatic to debilitating, one family member vs many…
Mito workup

- Clinical: Waxing and waning, Regression & progression, Low energy & easy fatigability
- Metabolic markers in blood and urine
- Mitochondrial and nuclear DNA testing
- Whole Exome/Genome sequencing
Mito treatment

- Regular Nutrition
- Regular Exercise/Therapy
- Optimized vitamin cocktail
G-tube metamorphosis
G-tube metamorphosis
<table>
<thead>
<tr>
<th>Section</th>
<th>Name</th>
<th>Per</th>
<th>Teacher</th>
<th>1-1-9</th>
<th>2-2-9</th>
<th>2-S1</th>
<th>3-3-9</th>
<th>4-4-9</th>
<th>4-S2</th>
<th>4-YA</th>
</tr>
</thead>
<tbody>
<tr>
<td>110102.08</td>
<td>COMPUTER</td>
<td>6</td>
<td>Jones, Cindy</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>132128.20</td>
<td>SPED READING</td>
<td>4r</td>
<td>Moore, Darlean</td>
<td>49 F</td>
<td>69 D</td>
<td>59 F</td>
<td>68 D</td>
<td>61 F</td>
<td>65 D</td>
<td>62 F</td>
</tr>
<tr>
<td>132129.20</td>
<td>SPED LANG</td>
<td>5r</td>
<td>Moore, Darlean</td>
<td>53 F</td>
<td>62 F</td>
<td>58 F</td>
<td>56 F</td>
<td>58 F</td>
<td>57 F</td>
<td>58 F</td>
</tr>
<tr>
<td>132149.01</td>
<td>SPED MATH</td>
<td>3r</td>
<td>Moore, Darlean</td>
<td>53 F</td>
<td>54 F</td>
<td>54 F</td>
<td>58 F</td>
<td>65 D</td>
<td>62 F</td>
<td>58 F</td>
</tr>
<tr>
<td>349901.08</td>
<td>HEALTH</td>
<td>7</td>
<td>Thomas, Heather</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>349902.08</td>
<td>PE</td>
<td>6</td>
<td>Capers, Lavon</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>409904.20</td>
<td>SCIENCE</td>
<td>1</td>
<td>Thomas, Heather</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>459901.31</td>
<td>SOC STUDIES</td>
<td>2</td>
<td>Thomas, Heather</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>500710.08</td>
<td>ART</td>
<td>6</td>
<td>Nabors, Amanda K</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>509904.08</td>
<td>MUSIC</td>
<td>6</td>
<td>Bennett, Rene</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>555555.08</td>
<td>Library</td>
<td>6</td>
<td>High, Rhonda</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**GPA method**

<table>
<thead>
<tr>
<th>GPA method</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerical</td>
<td>Wt.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>YTD Crd</th>
<th>Cum Crd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr. Abs</td>
<td>16.00</td>
</tr>
<tr>
<td>Yr. Tdy</td>
<td>1.00</td>
</tr>
</tbody>
</table>
# Report Card

Vancleave Upper Elementary  
13901 Hwy 57  
Vancleave, MS 39565  
(228) 826-4188

Number: 9984029  
Grade: 4  
HR: 4 Yates  
HR Teacher: Yates, Missy  
Counselor: 

* = Withdrawn  
**Term:** SEM 1  
**Grd Period:** 2

<table>
<thead>
<tr>
<th>Section</th>
<th>Name</th>
<th>Per</th>
<th>Teacher</th>
<th>1-1-9</th>
<th>2-2-9</th>
<th>2-S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>110102.17</td>
<td>COMPUTER</td>
<td>4</td>
<td>Jones, Cindy</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>132103.01</td>
<td>COMMUNITY</td>
<td>8ls</td>
<td>Miller, Tammie</td>
<td>99 A</td>
<td>100 A</td>
<td>100 A</td>
</tr>
<tr>
<td>132128.02</td>
<td>SPED READING</td>
<td>1ls</td>
<td>Miller, Tammie</td>
<td>97 A</td>
<td>99 A</td>
<td>98 A</td>
</tr>
<tr>
<td>132129.06</td>
<td>SPED LANG</td>
<td>2ls</td>
<td>Miller, Tammie</td>
<td>100 A</td>
<td>96 A</td>
<td>98 A</td>
</tr>
<tr>
<td>132149.02</td>
<td>SPED MATH</td>
<td>3ls</td>
<td>Miller, Tammie</td>
<td>98 A</td>
<td>94 A</td>
<td>96 A</td>
</tr>
<tr>
<td>132158.02</td>
<td>SPED SOC ST</td>
<td>5ls</td>
<td>Miller, Tammie</td>
<td>98 A</td>
<td>100 A</td>
<td>99 A</td>
</tr>
<tr>
<td>132175.02</td>
<td>SPED SCIENCE</td>
<td>6ls</td>
<td>Miller, Tammie</td>
<td>96 A</td>
<td>100 A</td>
<td>98 A</td>
</tr>
<tr>
<td>349902.17</td>
<td>PE</td>
<td>4</td>
<td>Capers, Lavon</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>500710.17</td>
<td>ART</td>
<td>4</td>
<td>Nabors, Amanda K</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>509904.17</td>
<td>MUSIC</td>
<td>4</td>
<td>Bennett, Rene</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>555555.17</td>
<td>Library</td>
<td>4</td>
<td>High, Rhonda</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GPA method</th>
<th>Cumulative</th>
<th>YTD Crd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numeric</td>
<td>Wt.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cum Crd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr. Abs</td>
</tr>
<tr>
<td>Yr. Tdy</td>
</tr>
</tbody>
</table>

2012-13
Exercise

- Physical & Occupational therapies
- Regulate activities
- Take breaks to rest before feeling exhausted
- Extra dose of vitamins before sports
Mito treatment

- CoQ10, MitoQ, Lipoic, Folinic, etc.
- EPI-743/Bendavia (trials ongoing)
- Dysautonomia/Pain (Neurontin, Elavil, Lyrica)
- Antiemetics (Zofran/Phenergan cream)
- Prokinetics (Domperidone/Iberogast)
- Behavior/Memory (Vayarin/Namenda)
- IV infusions (D10, NS)
- IM injections (methyl-B12, folinic, NAC)
- Compounded and optimized individually
- Level in plasma & leukocytes
3-year-old female
Autism
Extreme hyperactivity
Very poor eye contact
Developmental delay

After 3 months of vitamins:
Longer attention span
Better eye contact
Improved development
Before & After IV dextrose
5-year-old male
Regression & Autism at 13 mo (MMR)
Mito complex I deficiency
Low energy & fatigue

**Impression**
On the ADOS-2, Nathaniel scored in the autism range. These findings need to be interpreted as part of a complete evaluation for autistic spectrum disorders. His mother reported that his behavior during the evaluation was typical.

**Vitamin cocktail started at 4½ yo**
Cognitive skills & language advanced
Fatigability decreased
Lost diagnosis of autism at 5 yo

Results from this evaluation indicate that presently, Nathaniel does not display criteria indicative of an autism spectrum disorder. While prior reports indicate that Nathaniel was previously observed to show signs and symptoms indicative of an autism spectrum disorder, in the context of language and other delays, current testing did not find clinically significant symptomatology relating to autism spectrum disorder.
NATE

grandma
Loved
Ai Dawn
NATE
Brothers with autism & mito

mtDNA mutation
boys, mother & grandmother
- 5-year-old female
- Autism
- Developmental delay
- Hypotonia
- Easy fatigability
- Waxing/waning energy
- 5-hour day naps
- **Complex III deficiency**

Vitamins improved energy levels & academic skills and reduced sleep requirement
7-year-old male
Developmental delay
Autism
Regression
Seizures
Diffuse pain
Fatigability
Ptosis
Immunodeficiency

Treatment increased energy
Academic skills improved
Monday

1. me
2. mean
3. bean
4. be
5. beet
6. feet
7. low
8. road
9. who
10. door

I write with my pencil.

* with short standard pencil

James - Monday

1. I
2. can
3. am
4. I love
5. to go
down
6. stairs:
   (I love to go down stairs)
7. me
8. 2
9. 3
10. 4

* with adapted, weighted pencil
Write the numerals and the number words.

6  six  seis  7  seven  siete

8  eight  ocho  9  nine  nueve

10  ten  diez

teacher wrote over hand

later

10, 20, 30, 40, 50, 60, 70, 80, 90, 100
PROGNOSIS/POTENTIAL TO THERAPY: [ ] Poor [ ] Fair [X] Good [ ] Excellent

ASSESSMENT: James is a 6 year 8 month old male with a diagnosis of Autism who was referred to occupational therapy per orders from Kenneth Cruse, M.D. James shows delays in visual motor skills, manual dexterity, motor coordination, and self-care. During evaluation, he shows difficulty grasping a pencil, fastening buttons, and copying simple shapes. James would benefit from occupational therapy to address these areas of concern.

CURRENT STATUS:
Fine Motor:
Since October of 2011, James has met 3 of his 5 goals and continues to make great progress towards his remaining goals. He is now able to copy a triangle and square, don pants and shirt independently, and complete buttoning tasks. He has also made good progress in letter formation, control, size, and placement. James went from requiring moderate verbal cuing and assistance to complete writing activities to completing activities with minimal verbal cuing and demonstrations. James still has a difficult time holding writing utensil with a functional grasp. Several steps have been taken to correct his grasp; coban wrap to 4th and 5th digits, smaller pencils, coloring activity with very small crayons, verbal cuing and prompting. James presents with mild deficits with upper body motor coordination skills which may be contributing to the decreased coordination, stabilization and strength of grip.

DISCHARGE GUIDELINES
6-year-old female
Developmental delay
Autism
Low energy
Irritable bowel
Face flushing
Fatigability

Treatment increased energy
Academic performance advanced
sllam
mah mah man
pan pan ran
can can can
can pan pan
ran ran ran
ran ran ran
ran van van
5-year-old male
- Developmental delay
- Autism
- Carnitine deficiency
- Regression
- Hydrocephalus
- Low energy
- Fatigability

Treatment corrected carnitine
Fatigability decreased
Cognitive skills advanced
Counting Sheep - 1, 2, 3, 4

Trace. Write.

1 1 1 1 1 1 1

2 2 2 2 2 2

3 3 3 3

4 four

Counting Sheep - 1, 2, 3, 4

Trace. Write.

1 1 1 1 1 1 1

2 2 2 2 2 2

3 3 3 3

4 four
Summary

Genetics plays an important role in etiology of Autism

Chromosomal, single-gene and metabolic causes

Mitochondrial dysfunction accounts for a significant proportion of autistic patients and allows for effective and safe treatment

Genetic diagnosis aids early prevention, counseling on recurrence risks and appropriate treatment