

# **Genetics of Autism: From Chromosomes to Mitochondria**

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# 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%**

# Chromosomal



- 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 a verbal

Autism

Severe ID

**Karyotype** – trisomy 21

**Microarray:**

Chromosome 15q11.2 deletion

Maternal

# Single Gene Disorder



- Autism
- Developmental delay
- Facial gestalt
- 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

## ***Molecular Psychiatry* 17:290–314 (2012)**

- 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

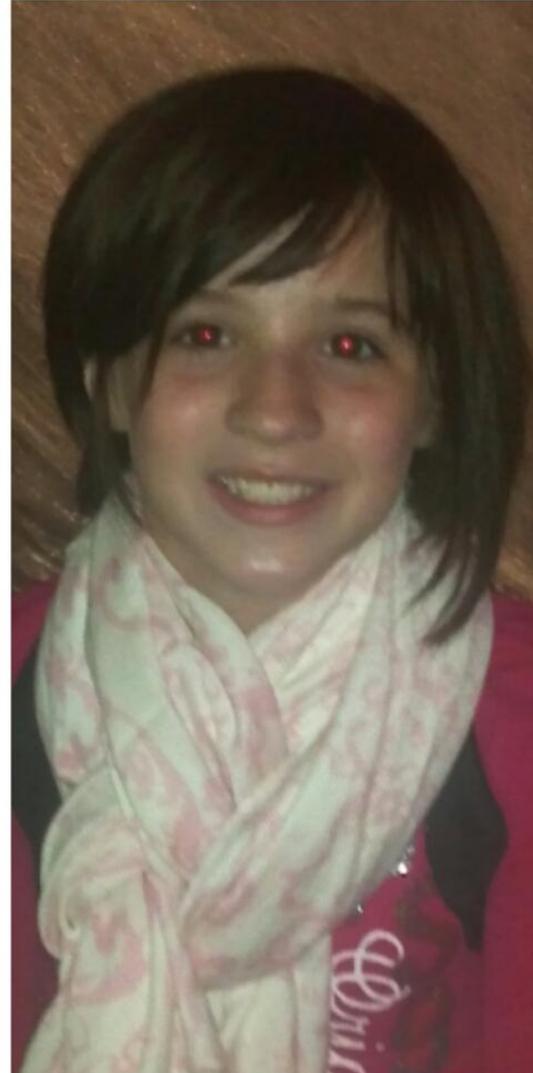
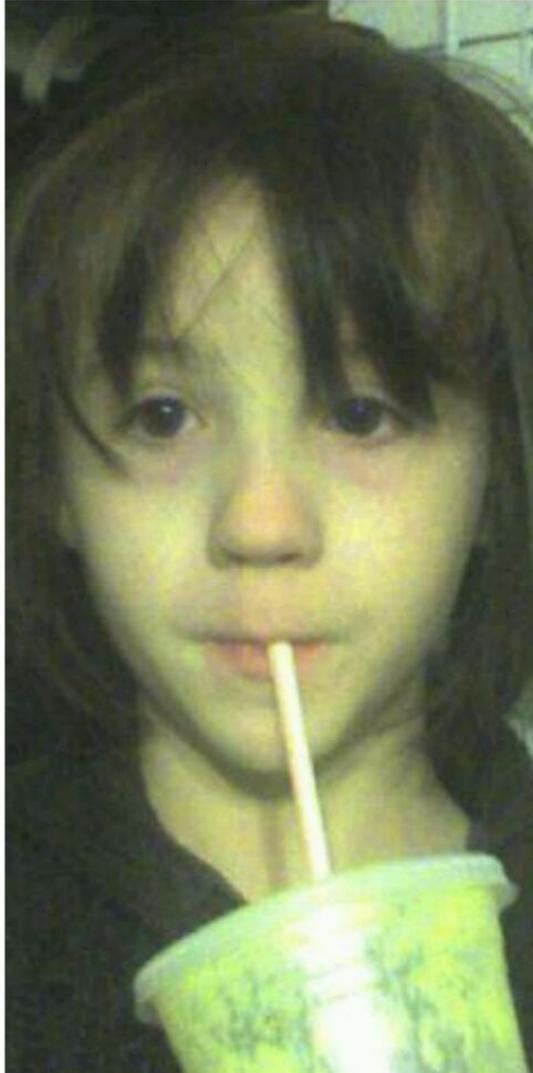
# Mito treatment

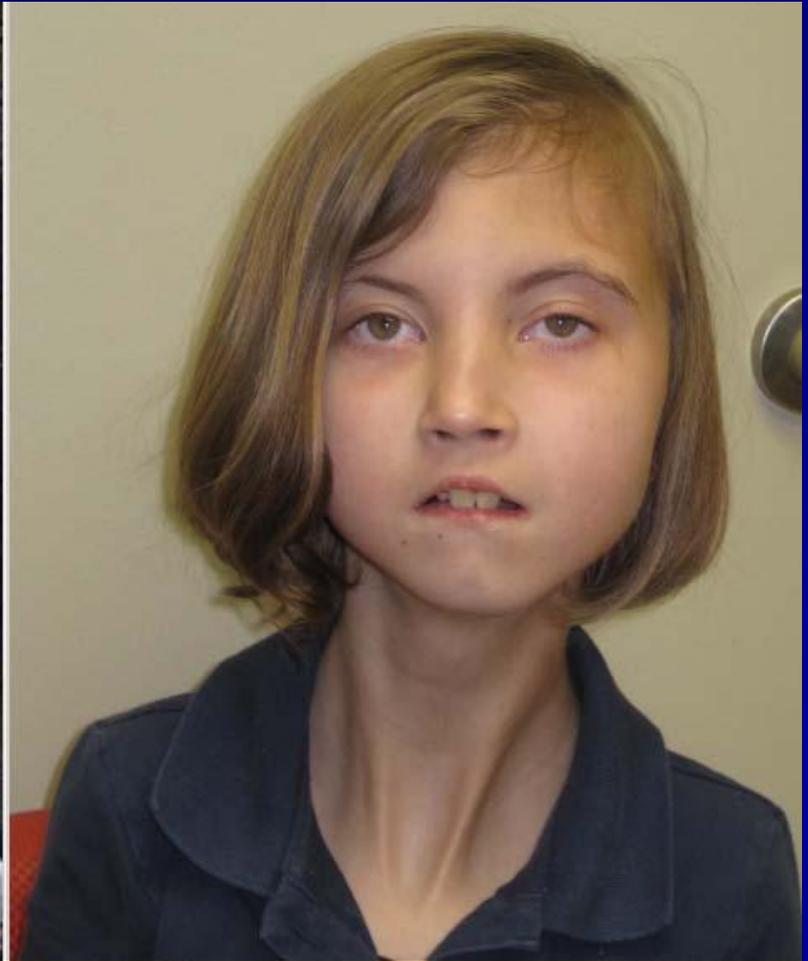
- Regular Nutrition
- Regular Exercise/Therapy
- Optimized vitamin cocktail

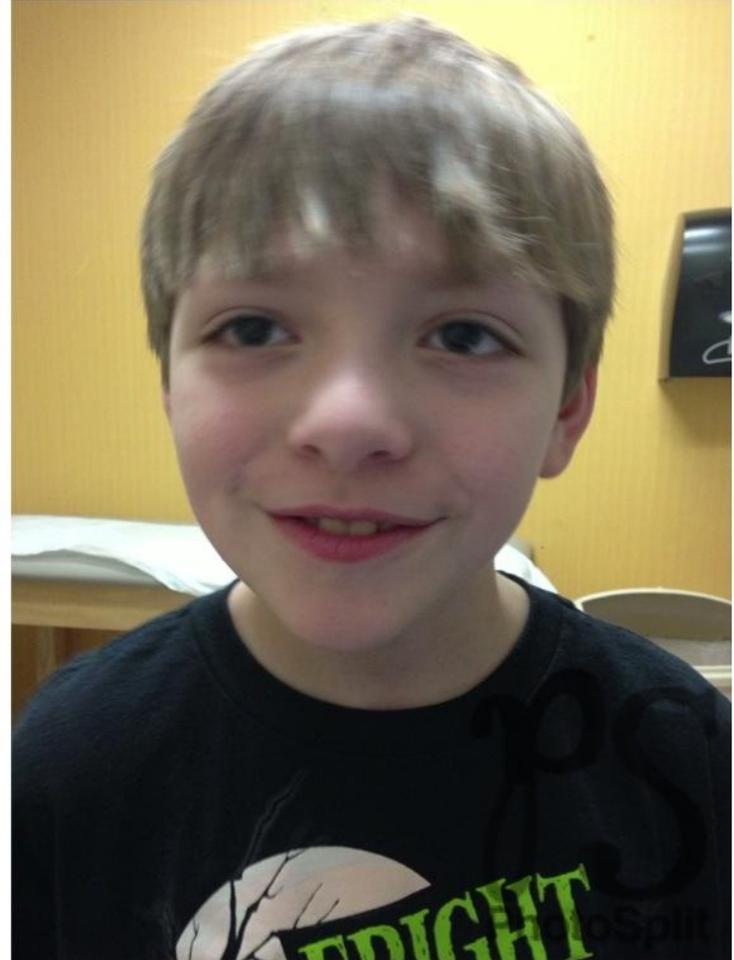
# G-tube metamorphosis



# G-tube metamorphosis









# G-tube metamorphosis



**Report Card**

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

**2011-12**

Number: 5984029

Grade: 3

HR: 0308 Thomas

HR Teacher: Thomas, Heather

Counselor:

\* = Withdrawn

Term: SEM 2

Grd Period: 4

Section	Name	Per	Teacher	1-1-9	2-2-9	2-S1	3-3-9	4-4-9	4-S2	4-YA
110102.08	COMPUTER	6	Jones, Cindy	S	S	S	S	S	S	S
132128.20	SPED READING	4r	Moore, Darlean	49 F	69 D	59 F	68 D	61 F	65 D	62 F
132129.20	SPED LANG	5r	Moore, Darlean	53 F	62 F	58 F	56 F	58 F	57 F	58 F
132149.01	SPED MATH	3r	Moore, Darlean	53 F	54 F	54 F	58 F	65 D	62 F	58 F
349901.08	HEALTH	7	Thomas, Heather	S	S	S	S	S	S	S
349902.08	PE	6	Capers, Lavon	S	S	S	S	S	S	S
409904.20	SCIENCE	1	Thomas, Heather	S	S	S	S	S	S	S
459901.31	SOC STUDIES	2	Thomas, Heather	S	S	S	S	S	S	S
500710.08	ART	6	Nabors, Amanda K	S	S	S	S	S	S	S
509904.08	MUSIC	6	Bennett, Rene	S	S	S	S	S	S	S
555555.08	Library	6	High, Rhonda	S	S	S	S	S	S	S

GPA method	Cumulative
	Wt.
Numeric	

YTD Crd	
Cum Crd	
Yr. Abs	16.00
Yr. Tdy	1.00

# Report Card

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

2012-13

Number: S984029  
Grade: 4  
HR: 4 Yates  
HR Teacher: Yates, Missy  
Counselor:

\* = Withdrawn

Term: SEM 1

Grd Period: 2

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

GPA method	Cumulative
	Wt.
Numeric	

YTD Crd	
Cum Crd	
Yr. Abs	6.00
Yr. Tdy	



# 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

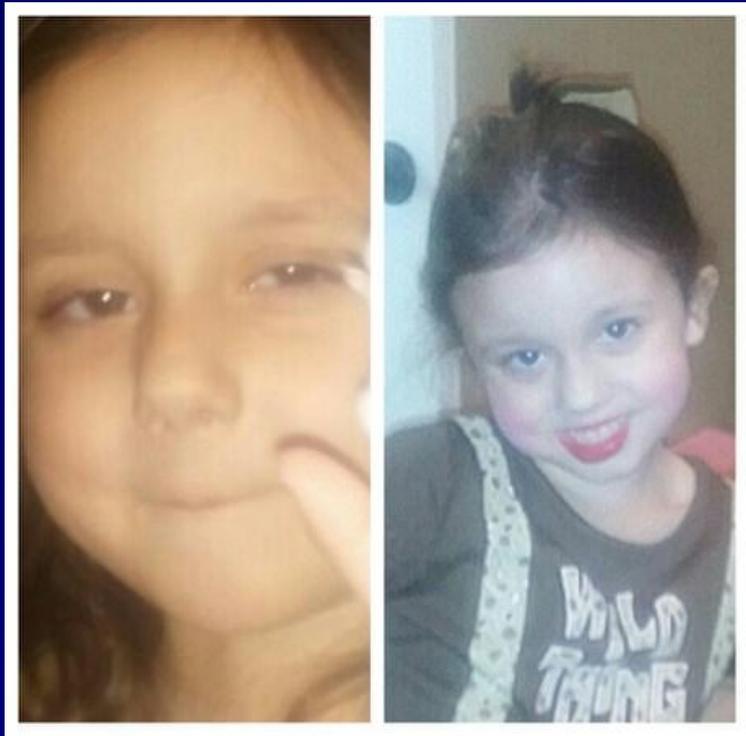


- 3-year-old female
- Autism
- Extreme hyperactivity
- Very poor eye contact
- Developmental delay



- **After 3 months of vitamins:**
- Longer attention span
- Better eye contact
- Improved development

# Before & After IV dextrose





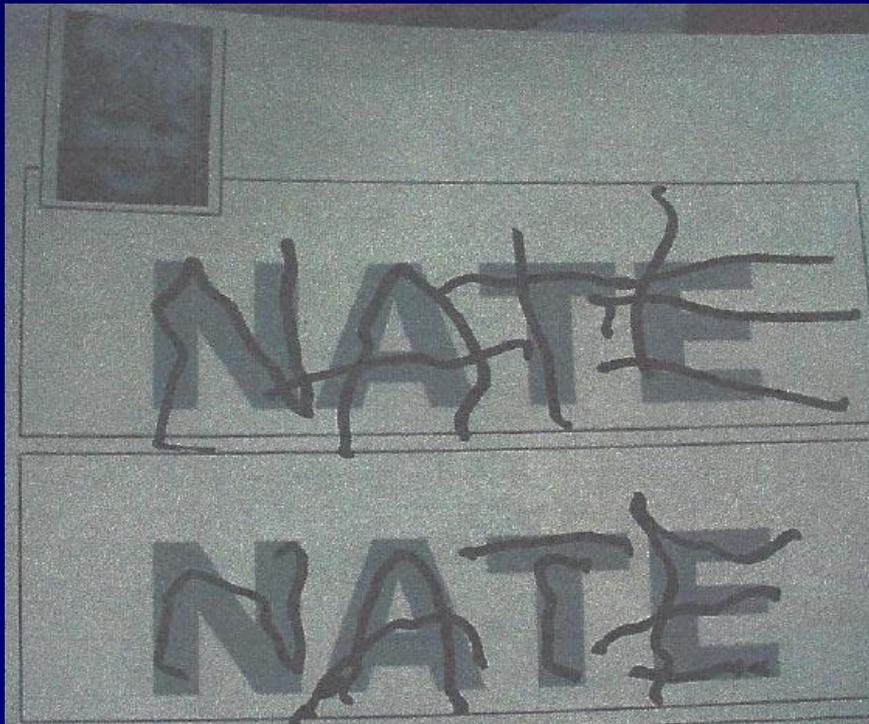
- 5-year-old male
- Regression & Autism at 13 mo (MMR)
- Mito complex I deficiency
- Low energy & fatigue

### 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.



grandma

LOVE

Aidan

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

01/23/18

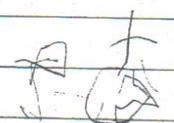
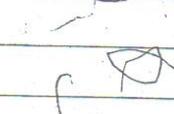
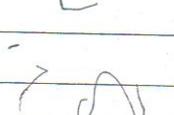
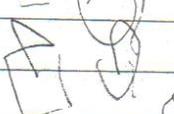
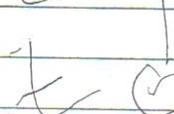
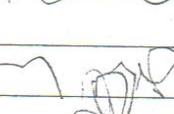
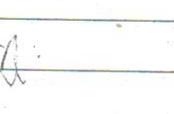
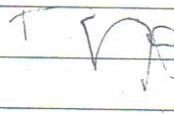
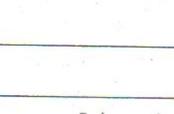
- 1 mean
- 2 bean
- 3 be
- 4 beet
- 5 feet
- 6 low
- 7 road
- 8 who
- 9 door

I write with my  
Pencil.

\* with short standard pencil

James - Monday

8/22

1. 
2. 
3. 
4.  I LOVE
5.  I LOVE
6.  I LOVE
7.  DOWN STAIRS
8.  DOWN STAIRS
9.  DOWN STAIRS
10.  DOWN STAIRS

{ I love to go down stairs }

\* with adapted, weighted pencil

Name James

Date Homework 0-2

Write the numerals and the number words.

09/11

w/weights

6 six seis 7 seven siete

6 six seis 7 seven siete

teacher wrote hand-over-hand

8 eight ocho 9 nine nueve

8 eight ocho 9 nine nueve

10 ten diez

10 ten diez



10, 20, 30, 40, 50, 60, 70, 80, 90, 100

**PROGNOSIS/POTENTIAL TO THERAPY:** Poor Fair 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.

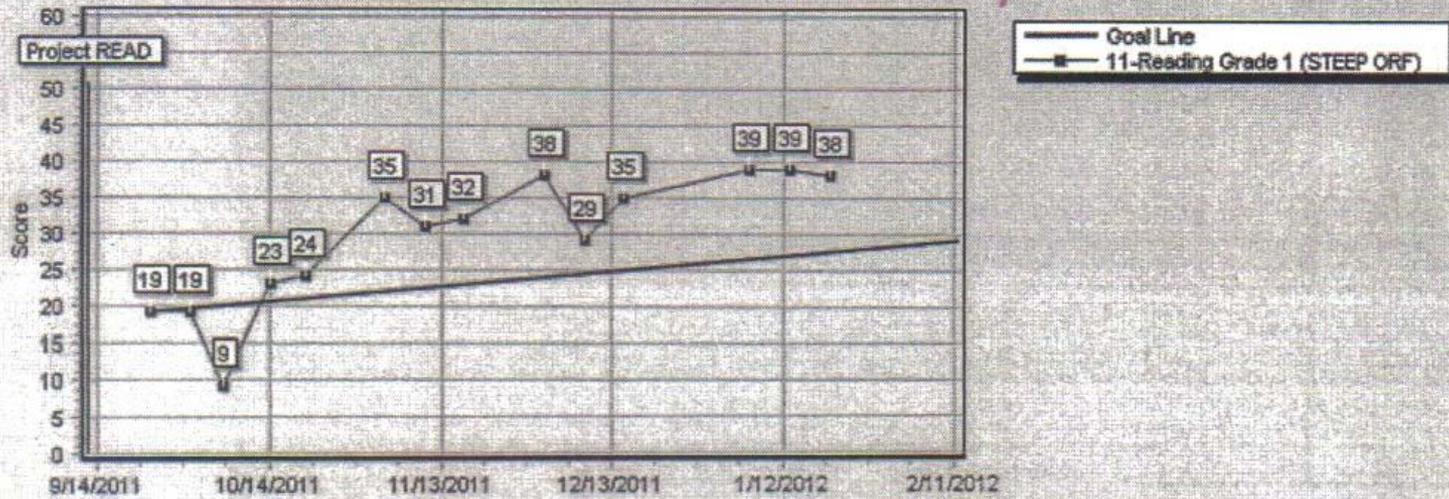
### **CURRENT STATUS:**

#### **Fine Motor:**

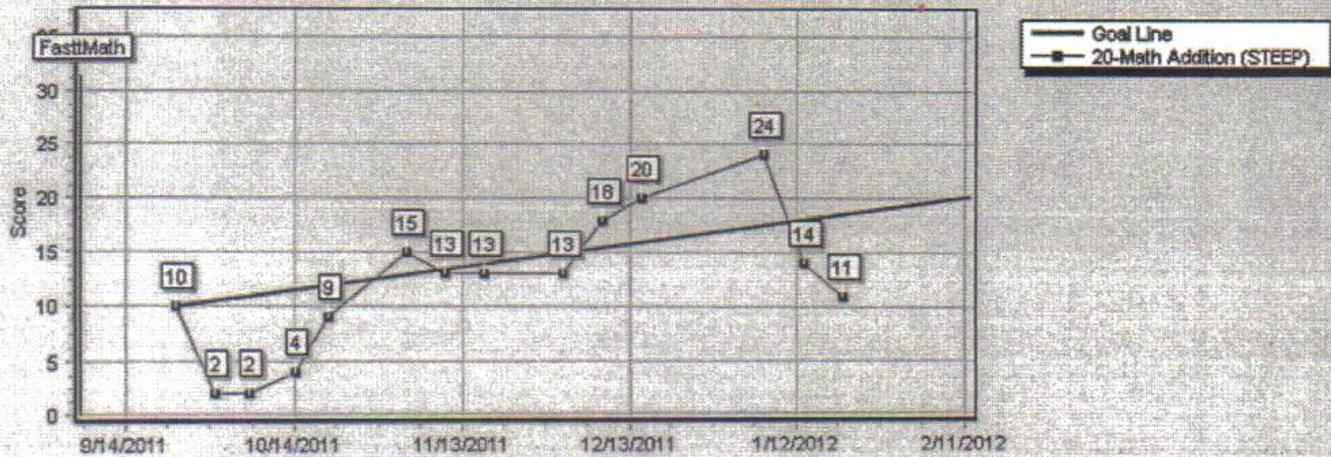
Since October of 2011, James has met 3 of his 5 goals and continues to make great progress towards his remaining goals. He is now able to copy a triangle and square, don pants and shirt independently, and complete buttoning tasks. He has also made good progress in letter formation, control, size, and 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 4<sup>th</sup> and 5<sup>th</sup> 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**

Monitoring	Progress
11-Reading Grade 1 (STEEP ORF)	1.38



Monitoring	Progress
20-Math Addition (STEEP)	0.79





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

**Treatment increased energy**  
**Academic performance advanced**

slonia

mah mah man

pan pan pan

can cahcan

fan fan fan

nan nan nan

van van van





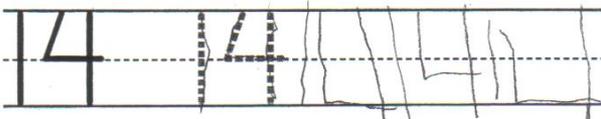
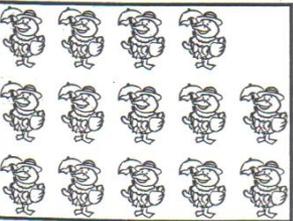
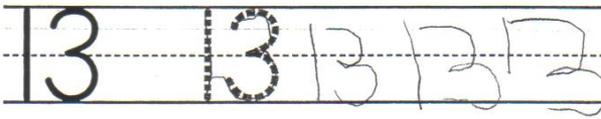
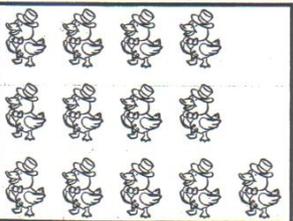
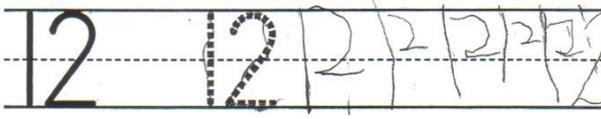
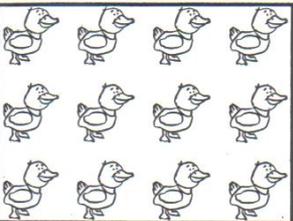
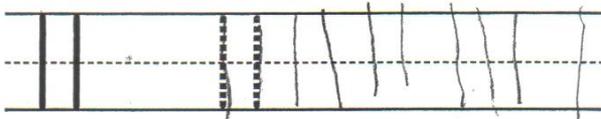
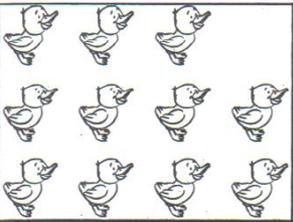
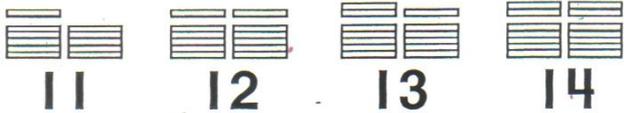
- 5-year-old male
- Developmental delay
- Autism
- Carnitine deficiency
- Regression
- Hydrocephalus
- Low energy
- Fatigability

**Treatment corrected carnitine**  
**Fatigability decreased**  
**Cognitive skills advanced**

M A T T H E W

# Just Ducky 11 - 14

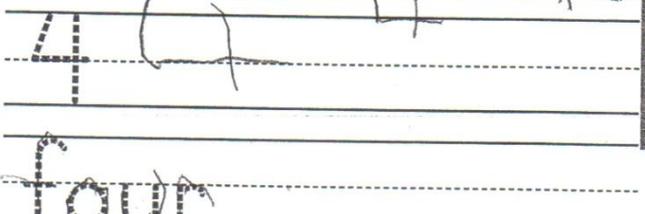
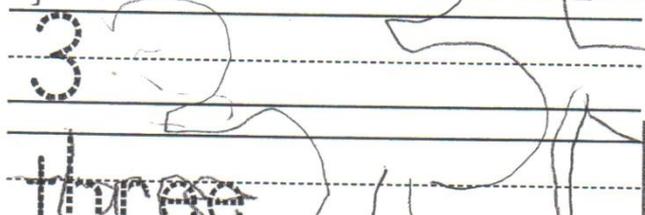
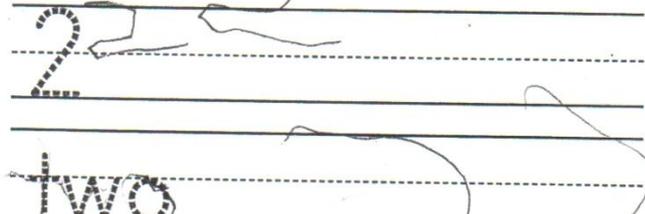
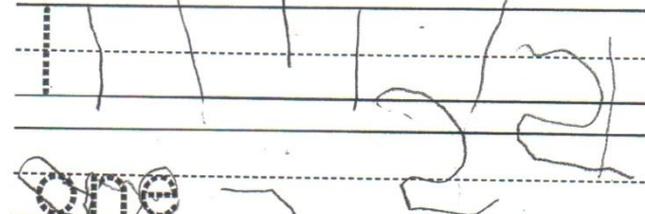
Count. Trace. Write.



H L A T T

# Counting Sheep - 1, 2, 3, 4

Trace. Write.



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