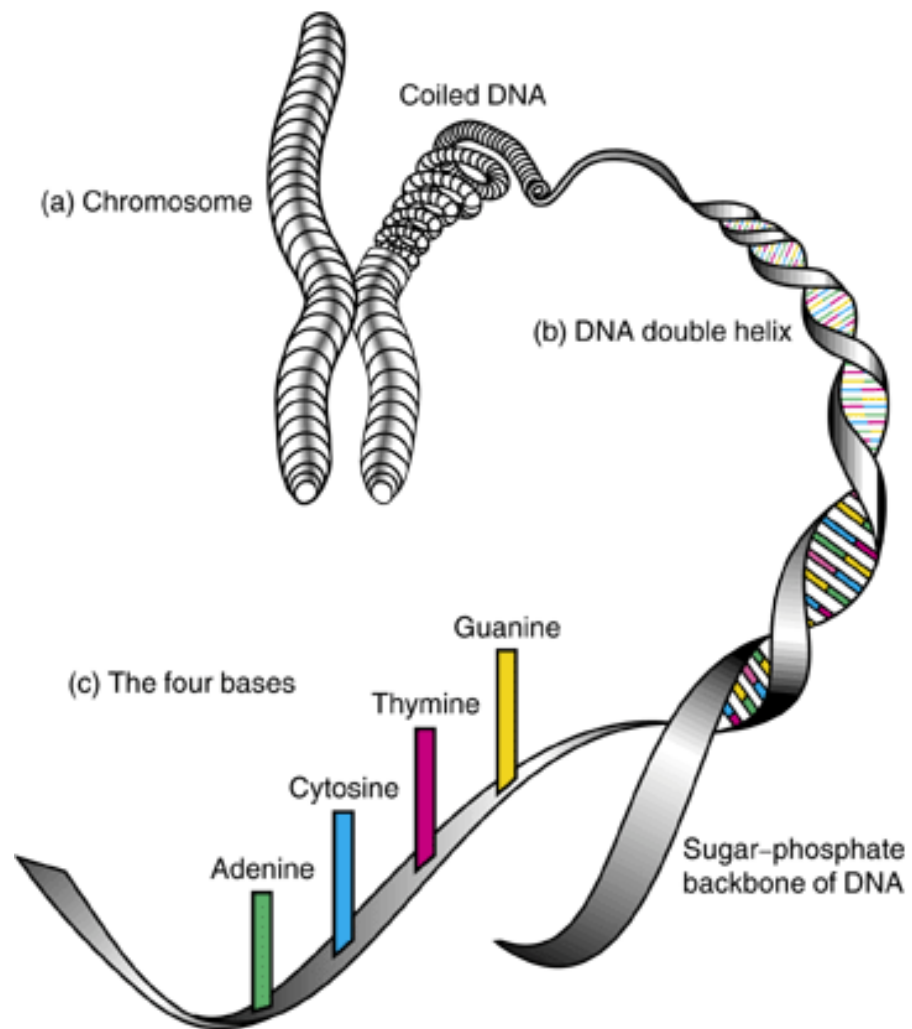


# Molecular Diagnostics for Genetic Diseases

Sean Hofherr, PhD, FACMG  
Director of Molecular Diagnostics  
Co-Director Biochemical Genetics  
Division of Laboratory Medicine

Mary Beth Seprish, MS, CGC  
Genetic Counselor  
Division of Laboratory Medicine

Kristina Cusmano-Ozog, MD, FACMG, FAAP  
Director Biochemical Genetics  
Co-Director Molecular Diagnostics  
Division of Laboratory Medicine  
Attending Physician  
Division of Genetics and Metabolism



# Growth of Clinical Genetics at Children's National

Huge increase in number of patients seen in the Division of Genetics and Metabolism

- 2009- 1,800
- 2016- 8,500

Correlates with large increase in new hires of ABMG Clinical Geneticists and CGCs

2009- 5 ABMG Clinical Geneticists and 5 CGCs

2016- 14 ABMG Clinical Geneticists and 18 CGCs

This resulted in an explosion of genetic testing at CN

# Genetic Testing at Children's National

6/2013- Molecular Diagnostics Laboratory in Division of Laboratory Medicine goes live with Chromosomal Microarray

© American College of Medical Genetics and Genomics**ACMG STANDARDS AND GUIDELINES**

Genetics  
inMedicine

**ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013**

Sarah T. South, PhD<sup>1,2</sup>, Charles Lee, PhD<sup>3</sup>, Allen N. Lamb, PhD<sup>1,2</sup>, Anne W. Higgins, PhD<sup>4</sup> and Hutton M. Kearney, PhD<sup>5</sup>; for the Working Group for the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee

Microarray methodologies, including array comparative genomic hybridization and single-nucleotide polymorphism-detecting arrays, are accepted as an appropriate first-tier test for the evaluation of imbalances associated with intellectual disability, autism, and multiple congenital anomalies. This technology also has applicability in prenatal specimens. To assist clinical laboratories in validation of

microarray methodologies for constitutional applications, the American College of Medical Genetics and Genomics has produced the following revised professional standards and guidelines.

*Genet Med* advance online publication 26 September 2013

**Key Words:** constitutional; guidelines; microarray; postnatal; prenatal; standards

# Genetic Testing at Children's National

6/2013- Molecular Diagnostics Laboratory in Division of Laboratory Medicine goes live with Chromosomal Microarray

8/2014- Transitioned to first and only FDA cleared Chromosomal Microarray

🏠 / News / FDA Clearance of Genetic Test for Developmental Delays and Intellectual Disabilities in Children

## Product News: FDA Clearance of Genetic Test for Developmental Delays and Intellectual Disabilities in Children

19 Mar 2014



**CytoScan® Dx Assay represents a technology leap over traditional postnatal genetic tests and significantly improves diagnostic capability**

Affymetrix, Inc. has announced that it has received 510(k) clearance from the U.S. Food and Drug Administration (FDA) to market its CytoScan® Dx Assay. This assay is intended for the postnatal detection of DNA copy number variants (CNV) in patients referred for chromosomal testing.

CytoScan Dx Assay is designed to help physicians diagnose children's developmental and intellectual disabilities more comprehensively by enabling a high-resolution genome-wide analysis of genetic aberrations. High resolution analysis can reveal small aberrations not readily seen using traditional techniques.



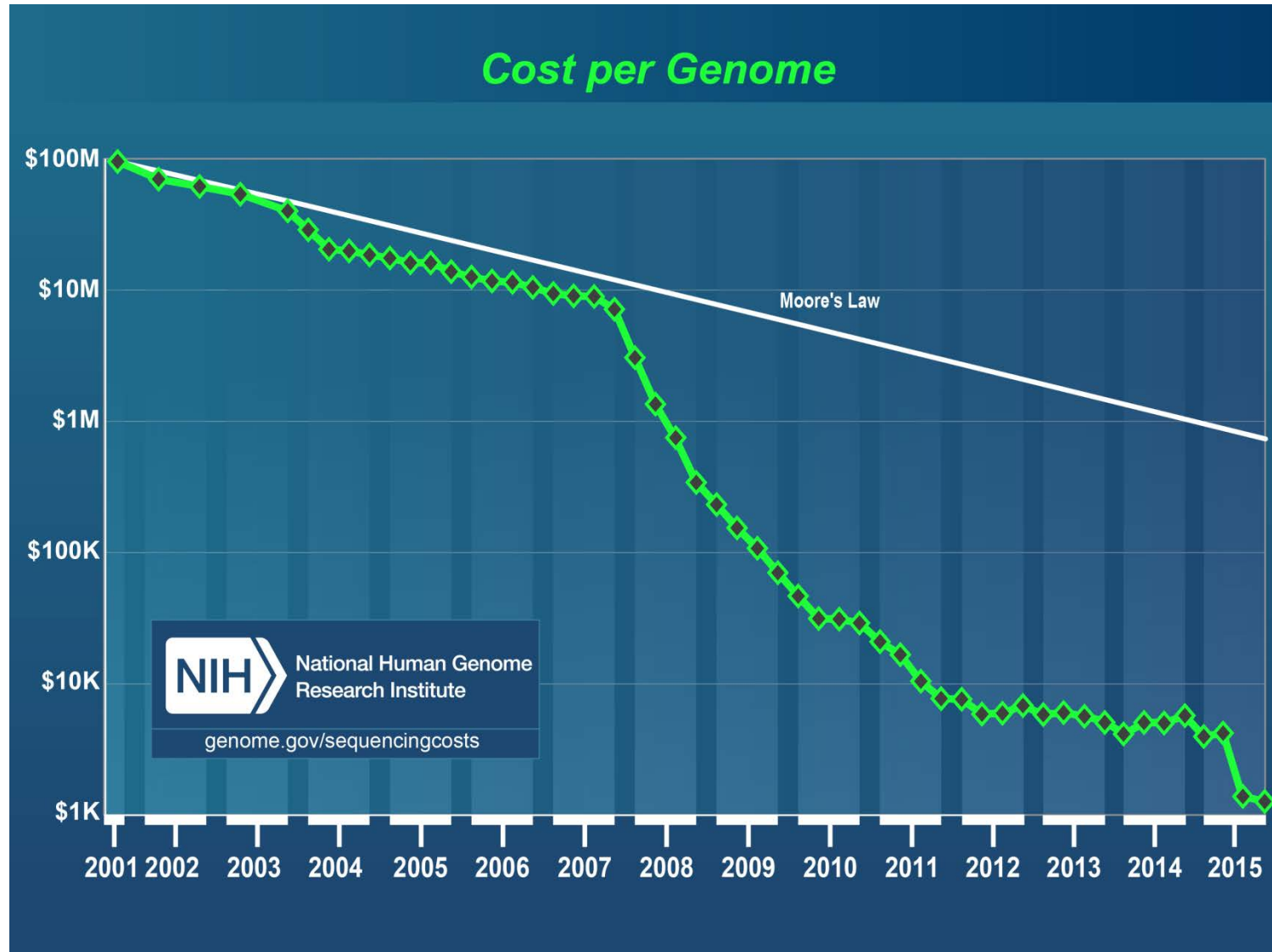
### CytoScan® Dx Assay

To aid in the diagnosis of developmental delay and intellectual disability



Unrivalled performance. Results that matter.

# Sequencing Advancements Driving Innovation





# Prior Options for Clinical Sequencing

Single gene sequencing

Small gene panels

Large gene panels

## Advantages

- Targeted to diagnose specific diseases or conditions
- Uncommon incidental findings
- Turn around time between 4-8 weeks

## Disadvantages

- A negative result will lead to a completely new test needing to be ordered
- Patient will need to come back in for recollect and insurance will be billed again for a totally new test
- No customization of testing to specific patient

Whole Exome Sequencing

Whole Genome Sequencing

## Advantages

- Comprehensive
- One test for all genes
- Unlikely to need an additional test ordered in immediate future
- Less money than ordering several other tests incrementally

## Disadvantages

- Possibilities for many incidental findings
- Variants of uncertain significance will be higher
- Genes of uncertain significance will be reported
- Long turn around time 4-6 months
- Very expensive for a single test



Children's National <sup>TM</sup>

# New Option for Sequencing Through CNMC

- 2/2015 Molecular Diagnostics Laboratory goes live with Clinical Personalized Sequencing Program
  - Using high throughput genomic sequencing we sequence all clinically relevant genes for every patient tested
  - We take a personalized approach to analyze and interpret only clinically relevant genes for that particular patient
    - Phenotype driven
    - Ability to leverage Chromosomal Microarray results to focus the analysis even further
  - If negative, additional genes to analyze can be added on, and since we have the data all we have to do is unmask the additional gene content



# Benefits to Patients, Physicians, and Lab

- Cost savings
  - Patient is billed less for initial test and any additional genes can be analyzed for a low cost
  - Laboratory can reduce interpretation costs and focus on variants in the genes that matter to the patient
- Shorter turn around time
  - Patient doesn't need to wait 4-6 months to get results
  - Currently 4-6 weeks
- Comprehensive
  - All clinically relevant genes are sequenced and additional genes can be analyzed for mutations rapidly by unmasking data
- Fewer incidental findings and variants of uncertain clinical significance
  - Patients analysis is customized to them, which yields less VUS results and no incidental findings
  - Laboratory spends less money on the interpretations and confirmations since the analysis is focused on clinically relevant genes

# Ordering Process

# Ordering Process

- At present, we are really only accepting samples on patients in CNHS.
  - Hopefully this will change soon!
- Therefore, the best approach for our community pediatricians to have genetic testing done through CNHS is to refer your patient to the Genetics Department. This referral also includes the added benefits of:
  - Pre- AND post-test genetic counseling
  - Insurance authorization
    - Our lab offers the ability to extract and hold DNA at the time of the initial genetic visit. Therefore, when authorization is obtained, the family doesn't have to come back for a separate blood draw.

or provide at least 2 of the following:

Name: \_\_\_\_\_

DOB:

MRN:

Insurance company (required):

Insurance Authorization (circle one): NOT REQUIRED or GRANTED

**If authorization was granted, please provide authorization number and time frame:**

Name of Primary Contact (physician, genetic counselor, nurse)	
---	--

Number for Primary Contact

### Clinical Indication and Family History

### Personalized Sequencing Panel Pre-Built Gene Lists (Select below):

Aplastic Anemia Panel
Comprehensive Brain Malformation Panel
Comprehensive Charcot-Marie-Tooth Panel
Comprehensive NeuroMuscular Panel
Congenital Disorders of Glycosylation Panel
Congenital Muscular Dystrophy Panel
Congenital Myasthenia syndrome Panel
Congenital Myopathy Panel
Congenital Disorders of Glycosylation Panel
Febrile Seizure Panel
Hemophagocytic Lymphohistiocytosis (HLH) Panel
Intellectual Disability / Autism Spectrum Disorder Panel
Microcephaly Panel
Nuclear Mitochondrial Gene Panel
Primary Ciliary Dyskinesia (PCD) Panel
Rett / Angelman syndrome Panel
X-linked Intellectual Disability Panel

Personalized Sequencing Panel Custom Gene List (write gene list below)

Personalized Sequencing Panels - MUST be discussed with Molecular Lab

PSPGL	Personalized Sequencing Panel by Gene List. Select either pre-built gene list or custom gene list in right column. If selecting a custom gene list, please either list genes, attach a gene list to this requisition, or email the list to the LabMed Genetic Counselors.
PSPP	Personalized Sequencing Panel by Phenotype. Clinical indication MUST be completed. Please allow 2-3 days for gene list to be generated.

## Parental Testing

		Chromosome Microarray Parental Testing must attach the child's test results or include the following information:
		Child's Name:
		Child's MRN:
		NGS Parental Testing must attach the child's test results or include the following information:

**Ethnicity (check all that apply)**

	African American
	Asian
	European Caucasian
	Hispanic
	Middle Eastern
	Native American
	Pacific Islander
	Undefined

\*Required Field

Questions/concerns can be addressed by contacting the Molecular Lab at x2631

# Personalized Sequencing Panels (PSP)

## PSP by Gene List

- Physician provides gene list
- Lab determines:
  - Is gene available for sequencing
  - Is gene well covered

## PSP by Phenotype

- Physician provides a phenotype
- Lab generates a gene list using:
  - HPO
  - OMIM
  - PubMed
  - GeneTests
  - Other labs panels
  - Regions of homozygosity and/or CNVs (determined by chromosomal microarray)
- Lab determines:
  - Is gene available for sequencing
  - Is gene well covered

# Personalized Sequencing Panels (PSP)

- Pricing based on number of genes
  - 1 gene
  - 2-5 genes
  - 6-15 genes
  - 16-50 genes
  - 51-100 genes
  - 101-150 genes
  - 151-200 genes
  - 201-250 genes
  - 251-300 genes
  - 301-500 genes
- If additional genes are requested, as long as the total # of genes stays within the same bracket a second analysis is available free of charge
- If the additional genes requested requires jumping to a different bracket (or if we have already done one free second analysis) then a minimal charge is associated with adding on additional genes that equals the difference between two brackets

# Genes associated with Autism

Editing Order: W1111\_L1111111111\_11111111\_MO0026

Test Creation

Test Review

Patient Name:DUMMY,CUSTOM  
MRN:111111111  
Ordering Physician:HOFHERR,SEAN  
Clinical Indication:-

Date of Birth:1975-06-08  
Accession Number:W1111  
Order Date:02/16/2015

Age:39y8m  
Container ID:L111111111  
Order Started By:HOFHERR,SEAN

Sex:Female  
Case Number:-

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

autism

Filter

Reset

Autism (154 genes)

► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☒ **ACSL4** (Phenotype:Autism)
- ☐ **ADSL** (Phenotype:Autism)
- ☐ **AGTR2** (Phenotype:Autism)
- ☐ **ALDH5A1** (Phenotype:Autism)
- ☐ **ALG13** (Phenotype:Autism)
- ☐ **ALMS1** (Phenotype:Autism)
- ☐ **ARHGEF6** (Phenotype:Autism)
- ☐ **ARX** (Phenotype:Autism)
- ☐ **ATRX** (Phenotype:Autism)
- ☐ **AUTS2** (Phenotype:Autism)
- ☐ **CACNG2** (Phenotype:Autism)
- ☐ **CASK** (Phenotype:Autism)
- ☐ **CDH15** (Phenotype:Autism)
- ☐ **CDKL5** (Phenotype:Autism)
- ☒ **CHD7** (Phenotype:Autism)
- ☐ **CHRNA7** (Phenotype:Autism)

154 Genes

122 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel



# ACSL4 vs CHD7

## *ACSL4 (X-linked Mental Retardation, type 68)*

- X-linked Inheritance
- Phenotype: nonsyndromic, intellectual disability and autism in males
- Females have highly variable cognitive capacities, ranging from moderate mental retardation to normal intelligence depending on her lyonization.

## *CHD7 (CHARGE syndrome)*

- Autosomal Dominant Inheritance
- Phenotype: coloboma, hear defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies
- Autism included in the phenotype, but certainly not the main feature

# Genes associated with Developmental Delay

Editing Order: W1111\_L111111111\_11111111\_MO0026

Test Creation Test Review

Patient Name:DUMMY,CUSTOM  
MRN:111111111  
Ordering Physician:HOFHERR,SEAN  
Clinical Indication:-

Date of Birth:1975-06-08  
Accession Number:W1111  
Order Date:02/16/2015

Age:39y8m  
Container ID:L111111111  
Order Started By:HOFHERR,SEAN

Sex:Female  
Case Number:-

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

developmental delay

Filter

Reset

Global developmental delay (919 genes)  
Mild global developmental delay (10 genes)  
Moderate global developmental delay (1 gene)  
Profound global developmental delay (1 gene)  
Severe global developmental delay (103 genes)

► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ AAAS (Phenotype:Global developmental delay)
- ☐ AARS (Phenotype:Global developmental delay)
- ☐ ABAT (Phenotype:Global developmental delay)
- ☐ ABCC8 (Phenotype:Global developmental delay)
- ☐ ABCD1 (Phenotype:Global developmental delay)
- ☐ ABCD4 (Phenotype:Global developmental delay)
- ☐ ACADM (Phenotype:Global developmental delay)
- ☐ ACADS (Phenotype:Global developmental delay)
- ☐ ACADSB (Phenotype:Global developmental delay)
- ☐ ACAT2 (Phenotype:Global developmental delay)
- ☐ ACSF3 (Phenotype:Global developmental delay)
- ☐ ACSL4 (Phenotype:Global developmental delay)
- ☐ ACTA2 (Phenotype:Global developmental delay)
- ☐ ACTB (Phenotype:Global developmental delay)
- ☐ ACTG1 (Phenotype:Global developmental delay)
- ☐ ACY1 (Phenotype:Global developmental delay)

919 Genes

703 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel

# Genes associated with Speech Delay

Editing Order: W1111\_L111111111\_11111111\_MO0026

Test Creation Test Review

Patient Name: DUMMY, CUSTOM  
MRN: 111111111  
Ordering Physician: HOFHERR, SEAN  
Clinical Indication: -

Date of Birth: 1975-06-08  
Accession Number: W1111  
Order Date: 02/16/2015

Age: 39y8m  
Container ID: L111111111  
Order Started By: HOFHERR, SEAN

Sex: Female  
Case Number: -

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

delayed speech

Filter

Reset

Delayed speech and language development (344 genes)



► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ AAAS (Phenotype: Global developmental delay)
- ☐ AARS (Phenotype: Global developmental delay)
- ☐ ABAT (Phenotype: Global developmental delay)
- ☐ ABCC8 (Phenotype: Global developmental delay)
- ☐ ABCD1 (Phenotype: Global developmental delay)
- ☐ ABCD4 (Phenotype: Global developmental delay)
- ☐ ACADM (Phenotype: Global developmental delay)
- ☐ ACADS (Phenotype: Global developmental delay)
- ☐ ACADSB (Phenotype: Global developmental delay)
- ☐ ACAT2 (Phenotype: Global developmental delay)
- ☐ ACSF3 (Phenotype: Global developmental delay)
- ☐ ACSL4 (Phenotype: Global developmental delay)
- ☐ ACTA2 (Phenotype: Global developmental delay)
- ☐ ACTB (Phenotype: Global developmental delay)
- ☐ ACTG1 (Phenotype: Global developmental delay)
- ☐ ACY1 (Phenotype: Global developmental delay)

919 Genes

703 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel

# Genes associated with Motor Delay

Editing Order: W1111\_L111111111\_111111111\_MO0026

Test Creation Test Review

Patient Name:DUMMY,CUSTOM  
MRN:111111111  
Ordering Physician:HOFHERR,SEAN  
Clinical Indication:-

Date of Birth:1975-06-08  
Accession Number:W1111  
Order Date:02/16/2015

Age:39y8m  
Container ID:L111111111  
Order Started By:HOFHERR,SEAN

Sex:Female  
Case Number:-

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

motor delay

Filter

Reset

Motor delay (369 genes)



► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ AAAS (Phenotype:Global developmental delay)
- ☐ AARS (Phenotype:Global developmental delay)
- ☐ ABAT (Phenotype:Global developmental delay)
- ☐ ABCC8 (Phenotype:Global developmental delay)
- ☐ ABCD1 (Phenotype:Global developmental delay)
- ☐ ABCD4 (Phenotype:Global developmental delay)
- ☐ ACADM (Phenotype:Global developmental delay)
- ☐ ACADS (Phenotype:Global developmental delay)
- ☐ ACADSB (Phenotype:Global developmental delay)
- ☐ ACAT2 (Phenotype:Global developmental delay)
- ☐ ACSF3 (Phenotype:Global developmental delay)
- ☐ ACSL4 (Phenotype:Global developmental delay)
- ☐ ACTA2 (Phenotype:Global developmental delay)
- ☐ ACTB (Phenotype:Global developmental delay)
- ☐ ACTG1 (Phenotype:Global developmental delay)
- ☐ ACY1 (Phenotype:Global developmental delay)

919 Genes

703 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel

# Child w/ developmental delay AND failure to thrive

Editing Order: W1111\_L111111111\_11111111\_M00026

Test Creation Test Review

Patient Name: DUMMY, CUSTOM  
MRN: 111111111  
Ordering Physician: HOFHERR, SEAN  
Clinical Indication: -

Date of Birth: 1975-06-08  
Accession Number: W1111  
Order Date: 02/16/2015

Age: 39y8m  
Container ID: L111111111  
Order Started By: HOFHERR, SEAN

Sex: Female  
Case Number: -

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel.

Phenotypes

failure to thrive

Filter

Reset

Failure to thrive (535 genes)

Failure to thrive in infancy (45 genes)

Failure to thrive secondary to recurrent infections (7 genes)

Severe failure to thrive (12 genes)

► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ AARS (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ABCD1 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ACADS (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ACSF3 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ADAR (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ADK (Phenotype: Global developmental delay, Failure to thrive)
- ☐ AHCY (Phenotype: Global developmental delay, Failure to thrive)
- ☐ AIMP1 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ALDH18A1 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ALG3 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ARFGEF2 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ASL (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ASNS (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ASS1 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ASXL1 (Phenotype: Global developmental delay, Failure to thrive)
- ☐ ATP5E (Phenotype: Global developmental delay, Failure to thrive)

306 Genes

232 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel

# Child with developmental delay, failure to thrive AND coloboma

Editing Order: W1111\_L111111111\_11111111\_MO0026

**Test Creation** | Test Review

Patient Name: DUMMY, CUSTOM      Date of Birth: 1975-06-08      Age: 39y8m      Sex: Female  
MRN: 111111111      Accession Number: W1111      Container ID: L111111111      Case Number: -  
Ordering Physician: HOFHERR, SEAN      Order Date: 02/16/2015      Order Started By: HOFHERR, SEAN  
Clinical Indication: -

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

- Chorioretinal coloboma (56 genes)
- Ciliary body coloboma (2 genes)
- Coloboma (92 genes)**
- Irido-fundal coloboma (11 genes)
- Iris coloboma (129 genes)
- Lens coloboma (2 genes)
- Lower eyelid coloboma (5 genes)
- Macular coloboma (20 genes)
- Optic nerve coloboma (43 genes)
- Retinal coloboma (14 genes)
- Upper eyelid coloboma (7 genes)

► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

**Selected Genes**

- ☐ **BMP4** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **CC2D2A** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **CEP290** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **CREBBP** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **HRAS** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **KIF7** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **KRAS** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **NRAS** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **OFD1** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **TMEM138** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **TMEM216** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)
- ☐ **TMEM237** (Phenotype: Global developmental delay, Failure to thrive, Coloboma)

17 Genes  
12 Genes in TrusightOne  
☒ Only Show TrusightOne Genes



# Child with AOH on CMA

Editing Order: W1111\_L111111111\_11111111\_M00026

Test Creation

Test Review

Patient Name:DUMMY,CUSTOM

MRN:11111111

Ordering Physician:HOFHERR,SEAN

Clinical Indication:-

Date of Birth:1975-06-08

Accession Number:W1111

Order Date:02/16/2015

Age:39y8m

Container ID:L111111111

Order Started By:HOFHERR,SEAN

Sex:Female

Case Number:-

► Add a Gene List

► Add by Phenotype

► Add by Syndrome/Genetic Disorder

► Add Genes

▼ Add/Remove Genes by Regions of Interest

You can filter your list to contain only those genes in Regions of Interest.  
Click Import to upload a file containing this data.

Choose File

Import

	Type	Call	Chr	Start	End	Length (bp)
<input checked="" type="checkbox"/>	LOH	High Percent AOH	1	19021597	24531154	5,509,557
<input checked="" type="checkbox"/>	LOH	High Percent AOH	1	156343606	159817278	3,473,672
<input checked="" type="checkbox"/>	LOH	High Percent AOH	1	193475878	202204213	8,728,335
<input checked="" type="checkbox"/>	LOH	High Percent AOH	2	24654450	28687043	4,032,593

Select All

Unselect All

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ ADCY3 (ROI:2:24654450-28687043)
- ☐ ADIPOQ (ROI:3:183296542-187221936)
- ☐ AHSB (ROI:3:183296542-187221936)
- ☐ AKR7A2 (ROI:1:19021597-24531154)
- ☐ AKR7A3 (ROI:1:19021597-24531154)
- ☐ ALDH4A1 (ROI:1:19021597-24531154)
- ☐ ALG3 (ROI:3:183296542-187221936)
- ☐ ALPL (ROI:1:19021597-24531154)
- ☐ APOA1 (ROI:11:115114365-121994700)
- ☐ APOA4 (ROI:11:115114365-121994700)
- ☐ APOA5 (ROI:11:115114365-121994700)
- ☐ APOC3 (ROI:11:115114365-121994700)
- ☐ ARHGEF11 (ROI:1:156343606-159817278)
- ☐ ARHGEF12 (ROI:11:115114365-121994700)
- ☐ ASPM (ROI:1:193475878-202204213)
- ☐ BACE1 (ROI:11:115114365-121994700)

1101 Genes

152 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel



# Child with AOH on CMA

Editing Order: W1111\_L111111111\_11111111\_M00026

Test Creation Test Review

Patient Name:DUMMY,CUSTOM

MRN:111111111

Ordering Physician:HOFHERR,SEAN

Clinical Indication:-

Date of Birth:1975-06-08

Accession Number:W1111

Order Date:02/16/2015

Age:39y8m

Container ID:L111111111

Order Started By:HOFHERR,SEAN

Sex:Female

Case Number:-

► Add a Gene List

► Add by Phenotype

▼ Add by Syndrome/Genetic Disorder

You can choose from the set of syndromes below. Selecting a syndrome will add the relevant genes to the panel you are ordering. You may select multiple syndromes to add to your panel

Syndrome

Filter

Reset

☐ All ☐ Autosomal Dominant ☒ Autosomal Recessive ☐ X-Linked Dominant ☐ X-Linked Recessive

100100 ?Prune belly syndrome (1 gene)  
102700 Adenosine deaminase deficiency, partial (1 gene)  
102700 Severe combined immunodeficiency due to ADA deficiency (1 gene)  
103050 Adenylosuccinase deficiency (1 gene)  
107741 Hyperlipoproteinemia, type III (1 gene)  
107741 {Myocardial infarction susceptibility} (1 gene)  
113750 Albinism, oculocutaneous, type VI (1 gene)  
113750 [Skin/hair/eye pigmentation 4, fair/dark skin] (1 gene)  
116920 Leukocyte adhesion deficiency (1 gene)  
124000 Mitochondrial complex III deficiency, nuclear type 1 (1 gene)  
125400 Dentin dysplasia, type I, with microdontia and misshapen teeth (1 gene)  
130070 Ehlers-Danlos syndrome, progeroid type, 1 (1 gene)  
131200 {Endometriosis, susceptibility to, 1} (1 gene)  
133540 Cockayne syndrome, type B (1 gene)  
135400 Hypertrichosis terminalis, generalized, with or without gingival hyperplasia

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ **ALDH4A1** (Disease:239510 Hyperprolinemia, type II) (ROI:1:19021597-24531154)
- ☐ **ALG3** (Disease:601110 Congenital disorder of glycosylation, type Id) (ROI:3:183296542-187221936)
- ☐ **ALPL** (Disease:241510 Hypophosphatasia, childhood, 241500 Hypophosphatasia, infantile) (ROI:1:19021597-24531154)
- ☐ **ASPM** (Disease:608716 Microcephaly 5, primary, autosomal recessive) (ROI:1:193475878-202204213)
- ☐ **C1QA** (Disease:613652 C1q deficiency) (ROI:1:19021597-24531154)
- ☐ **C1QB** (Disease:613652 C1q deficiency) (ROI:1:19021597-24531154)
- ☐ **C1QC** (Disease:613652 C1q deficiency) (ROI:1:19021597-24531154)
- ☐ **CA2** (Disease:259730 Osteopetrosis, autosomal recessive 3, with renal tubular acidosis) (ROI:8:83376886-87696925)
- ☐ **CCT5** (Disease:256840 Neuropathy, hereditary sensory, with spastic paraplegia) (ROI:5:6926518-11835536)
- ☐ **CD3D** (Disease:615617 Immunodeficiency 19) (ROI:11:115114365-121994700)
- ☐ **CD3E** (Disease:615615 Immunodeficiency 18) (ROI:11:115114365-121994700)

60 Genes

52 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel

# Child with AOH on CMA and a phenotype of seizures

Editing Order: W1111\_L111111111\_11111111\_MO0026

Test Creation

Test Review

Patient Name: DUMMY, CUSTOM  
MRN: 111111111  
Ordering Physician: HOFHERR, SEAN  
Clinical Indication: -

Date of Birth: 1975-06-08  
Accession Number: W1111  
Order Date: 02/16/2015

Age: 39y8m  
Container ID: L111111111  
Order Started By: HOFHERR, SEAN

Sex: Female  
Case Number: -

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

seizure

Filter

Reset

Focal seizures (52 genes)

Focal seizures with impairment of consciousness or awareness (44 genes)

Focal seizures without impairment of consciousness or awareness (3 genes)

Focal seizures, afebrile (4 genes)

Generalized clonic seizures (2 genes)

Generalized myoclonic seizures (105 genes)

Generalized seizures (20 genes)

Generalized tonic seizures (27 genes)

Generalized tonic-clonic seizures (95 genes)

Generalized tonic-clonic seizures on awakening (7 genes)

Hemiclonic seizures (10 genes)

Hypocalcemic seizures (4 genes)

Hypoglycemic seizures (15 genes)

Photosensitive tonic-clonic seizures (1 gene)

Seizures (1029 genes)

► Add by Syndrome/Genetic Disorder

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ **ALDH4A1** (Phenotype: **Seizures**) (Disease: **239510 Hyperprolinemia, type II**) (ROI: 1:19021597-24531154)
- ☐ **ALG3** (Phenotype: **Seizures**) (Disease: **601110 Congenital disorder of glycosylation, type Id**) (ROI: 3:183296542-187221936)
- ☐ **ALPL** (Phenotype: **Seizures**) (Disease: **241510 Hypophosphatasia, childhood, 241500 Hypophosphatasia, infantile**) (ROI: 1:19021597-24531154)
- ☐ **ASPM** (Phenotype: **Seizures**) (Disease: **608716 Microcephaly 5, primary, autosomal recessive**) (ROI: 1:193475878-202204213)
- ☐ **CLCN2** (Phenotype: **Generalized myoclonic seizures, Febrile seizures, Focal seizures, Generalized tonic-clonic seizures on awakening, Generalized tonic-clonic seizures, Absence seizures**) (Disease: **615651 Leukoencephalopathy with ataxia**) (ROI: 3:183296542-187221936)
- ☐ **CRB1** (Phenotype: **Seizures**) (Disease: **600105 Retinitis pigmentosa-12, autosomal recessive**) (ROI: 1:193475878-202204213)
- ☐ **DPAGT1** (Phenotype: **Seizures**) (Disease: **608093 Congenital disorder of glycosylation, type Ij, 614750 Myasthenic syndrome, congenital, 13, with tubular aggregates**) (ROI: 11:115114365-121994700)
- ☐ **EIF2B4** (Phenotype: **Seizures**) (Disease: **603896 Leukoencephaly with**)

17 Genes

15 Genes in TrusightOne

☒ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

Save Order

Cancel

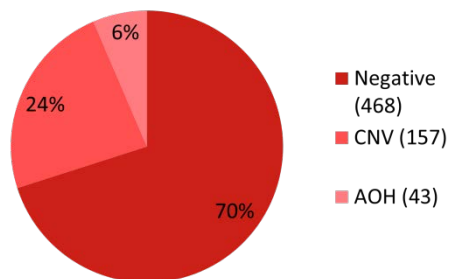


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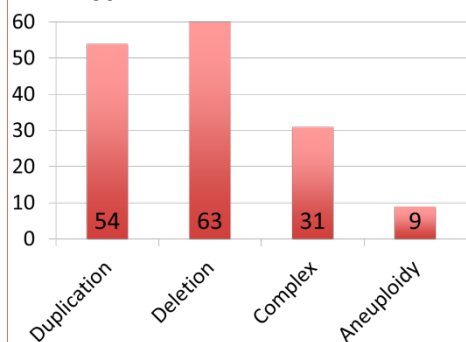
# CMA case examples

# CytoScan® Dx Assay: Our 1<sup>st</sup> year experience

**CMA Results**



**Types of CNVs Detected**



**AOH & Identity by descent**

	N
1 <sup>st</sup> degree relative	1
2 <sup>nd</sup> degree relative	8
3 <sup>rd</sup> degree relative	13
4 <sup>th</sup> degree relative	13

**AOH & UPD**

	N
Chr 7	2
Chr 14	4
Chr 15	2

**Common CNVs Identified**

	N
1q21 del	2
1q21 dup	2
3q13 del	1
5p15 del	1
5q35 del	1
5q35 dup	1
7q11 del	5
15q11 del	2
15q11 dup	2
16p11 dup	1
16p13 dup	2
17p11 del	1
17p11 dup	1
18p11 del	1
18p11 trip	1
18q22 del	3
22q11 del	6
22q11 dup	4
22q13 del	2

**Inheritance of CNVs**

	N
De novo	15
Maternal	29
Paternal	11

**Complex CNVs Identified**

1q44x4 1q44x3	Dup/Trip of 1q44
8p23.3p23.1x1 8p23.1p12x3	Derivative chromosome 8
15q13.2q13.3x1 16p11.2x1	15q13 AND 16p11 (220 kb, obesity) del syndromes
16p12.2x1 17p12x1	16p12 AND 17p12 (HNPP) del syndromes
22q11.1q11.21x4 22q11.21x3	Cat eye syndrome
Xq28x3 Xq28x4 Xq28x3	Complex X rearrangement

**Aneuploidy**

	N
Trisomy 13	1
Trisomy 18	2
Trisomy 21	1
47,XXY	2
47,XYY	2
48,XXYY	1
Mosaic Trisomy 14	1
Mosaic Turner	1



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# Is it 22q11?

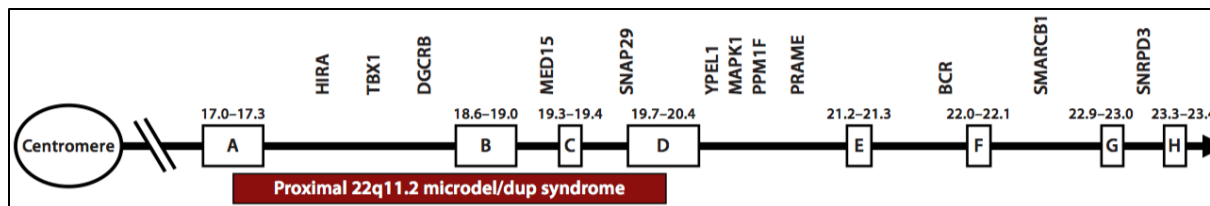
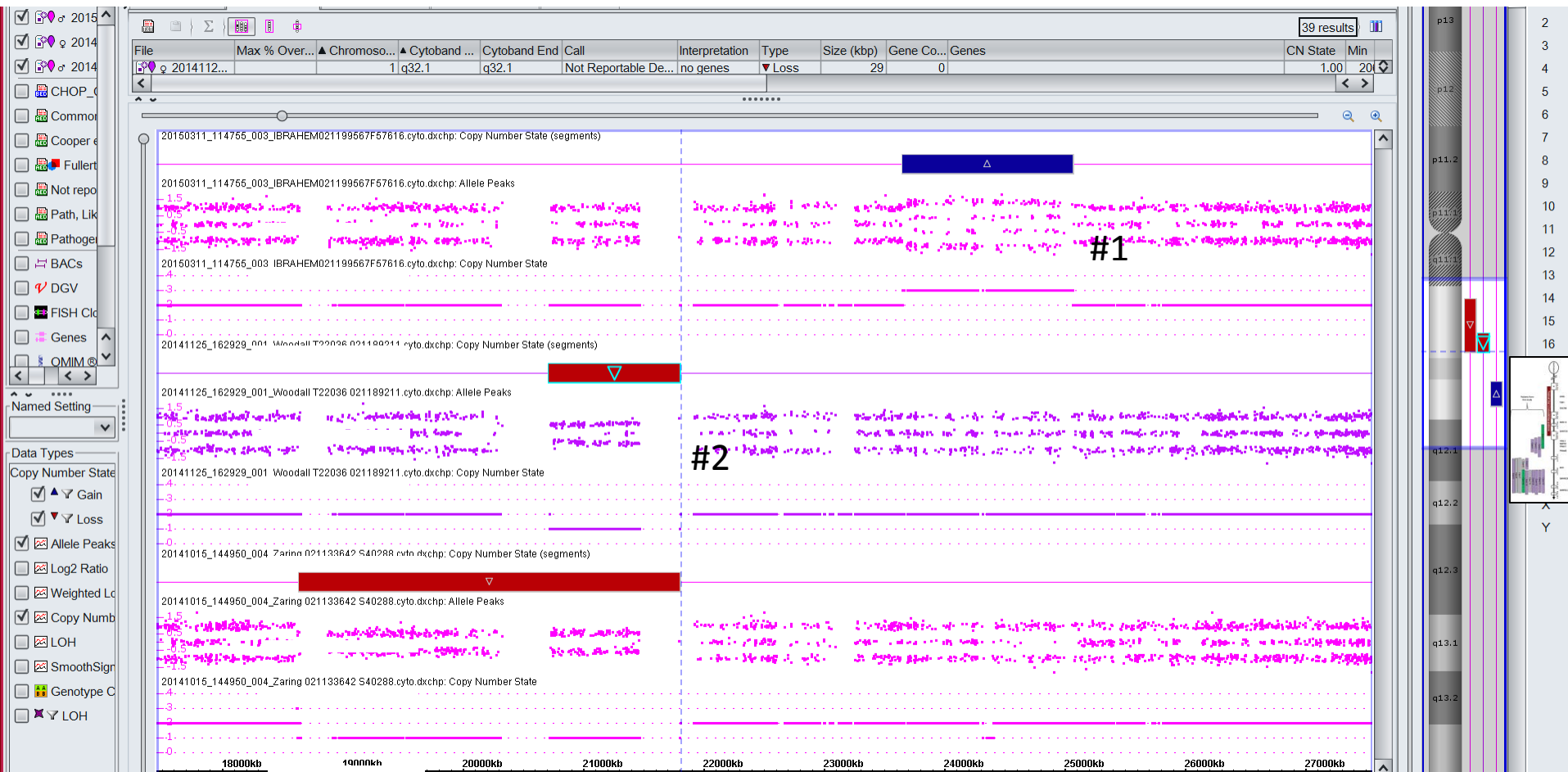
## Case Study #1

- 2.5 year old male
- Seen in clinic
- Developmental delay
- Limited speech
- Mild hypotonia

## Case Study #2

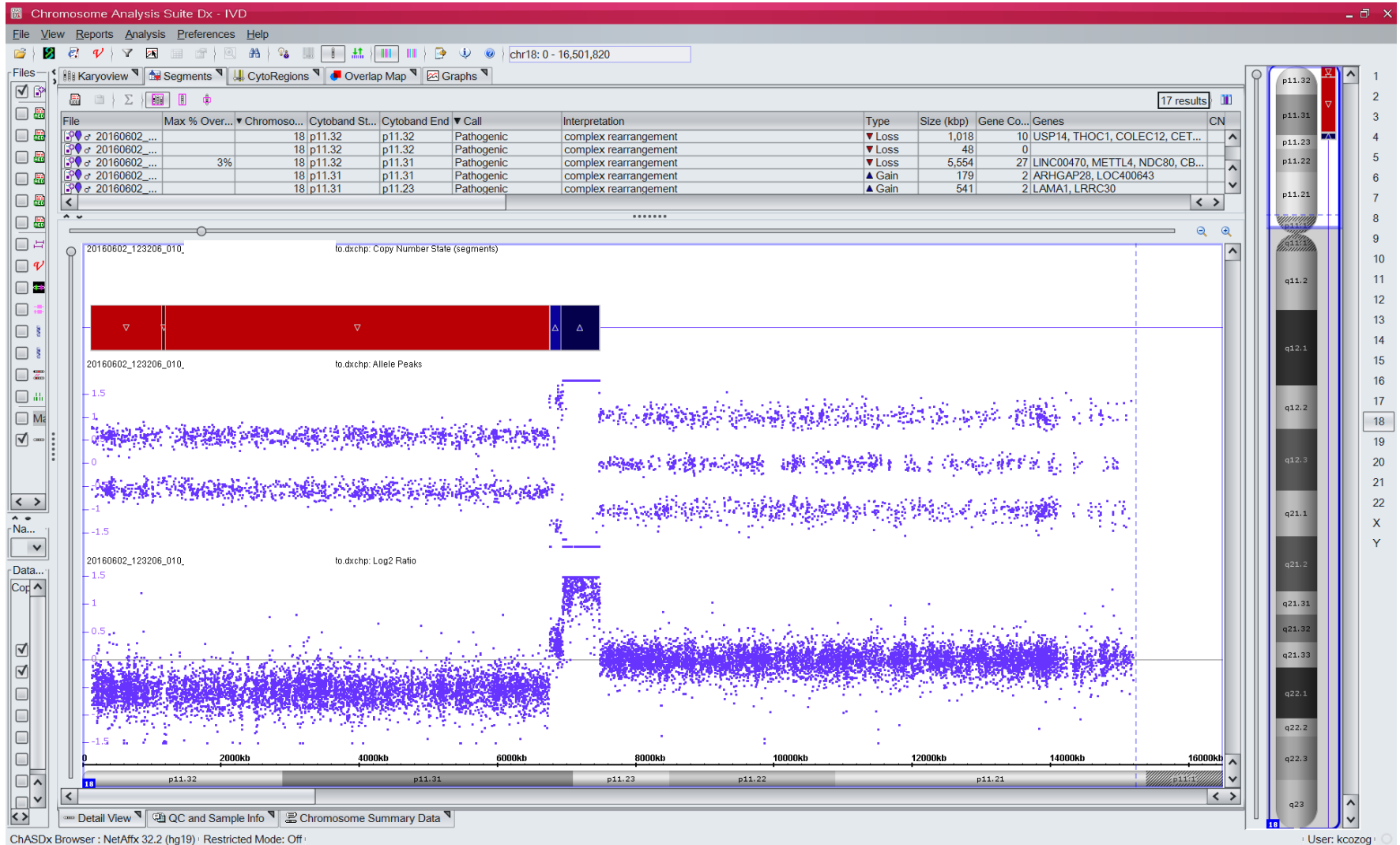
- 1 day old female
- Seen in NICU
- Prenatal diagnosis of TOF
- No additional malformations

# 22q11 – Array is better than FISH





# Array is better than FISH and Karyotype





# PWAS

## Case Study #3

- 4 day old male
- Seen in NICU
- Profound hypotonia
- No major malformations

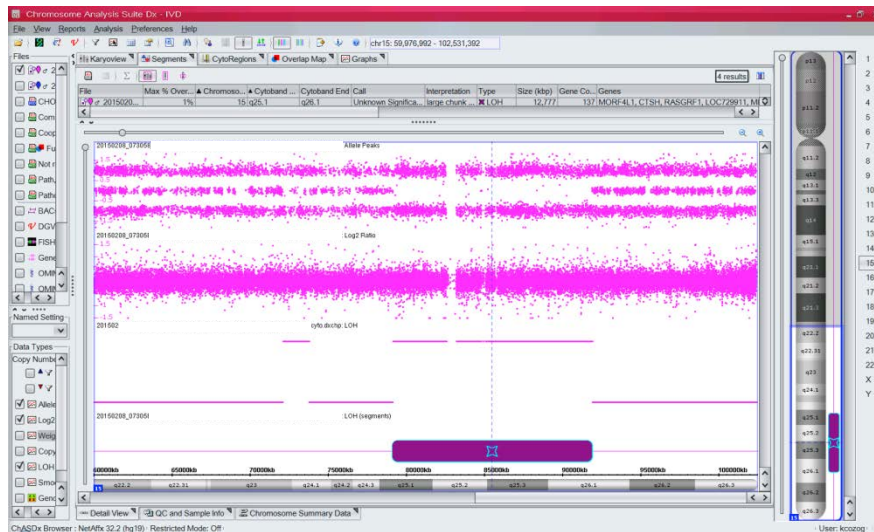
## Case Study #4

- 16 month old male
- Seen in clinic
- Developmental delays
- Happy demeanor
- Wide-based gait

# PWAS

# Case Study #3

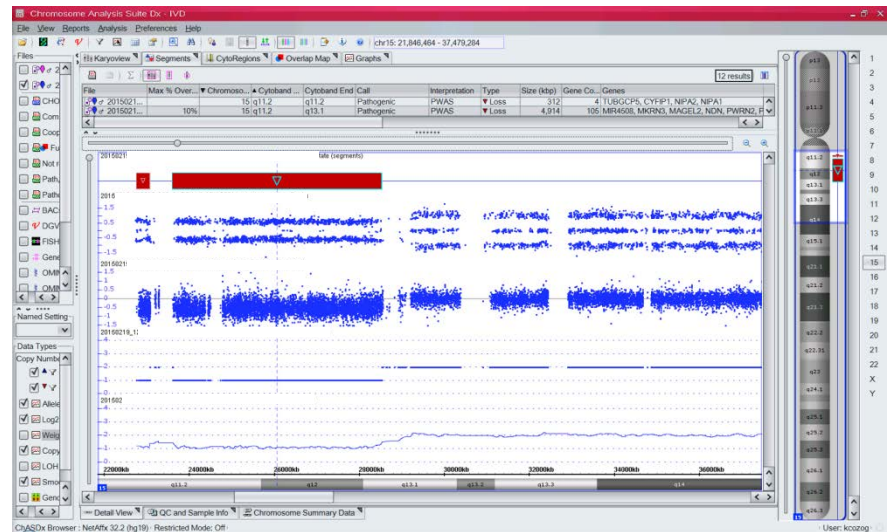
12.8Mb AOH at 15q25.1q26.1  
Concerning for UPD



## F/U methylation studies confirm PWS

# Case Study #4

## 5.8Mb deletion of 15q11.2q13.1



## Phenotype consistent with AS



# NGS case examples

# Case Example #1

- 4-month-old boy with encephalopathy, myoclonus, spasticity, diffuse cerebral volume loss, and central apnea seen in Genetics clinic for the first time.
- “I think the most cost-effective approach will be to obtain a Personalized Gene Panel sequencing for genes that have previously been associated with the aforementioned conditions, mainly early myoclonic encephalopathy. This Gene Panel will include the following genes: *STXBP1*, *ARX*, *SLC25A22*, *PNKP*, *AMT*, *GLDC*, *GCSH*, *GLYCTK*, *ABAT*, *ATP7A*, *ADSL*, *ARHGEF9*, *GLRA1*, *GLRB*, *SLC6A5*, *SETBP1* and *GPHN*.”
- Insurance authorization was obtained and testing was sent:

**RESULT SUMMARY:** NEGATIVE. No clinically relevant alterations were identified in this patient.

**CLINICAL INDICATION:** 7 month old male with encephalopathy, myoclonus, spasticity, diffuse cerebral volume loss, and central apnea.

**GENES ANALYZED\*:** ABAT, ADSL, AMT, ARHGEF9, ARX, ATP7A, GCSH, GLDC, GLRA1, GLRB, GLYCTK, GPHN, PNKP, SETBP1, SLC25A22, SLC6A5, STXBP1

\*See Limitations section for information regarding areas of low coverage.

# Case Example #1

- Return visit to Genetics: 11-month-old boy with a history of polyhydramnios in-utero, microcephaly, encephalopathy, stimulation myoclonus/excessive startle reflex, spasticity, central apnea and trichomegaly.
- “PAA and UOA have been normal in the past, as was a PSP including several genes known to be associated with a similar phenotype. At this point, I would like to add a few genes to the already sent PSP. “
- A **FREE** second look was obtained:

**RESULT SUMMARY:** POSITIVE. Testing identified that this patient is compound heterozygous for two variants in TSEN54. One of these variants is a known pathogenic mutation. The other variant is a likely pathogenic deletion of two basepairs. Homozygous and compound heterozygous mutations in TSEN54 have been associated with multiple forms of pontocerebellar hypoplasia (MIM#610204, 277470, 225753).

**CLINICAL INDICATION:** A Personalized Sequencing Panel is requested on an 11 month old male with a history of encephalopathy, myoclonus, spasticity, central apnea, and trichomegaly.

**GENES ANALYZED\*:** ALDH7A1, ASNS, ASXL1, B3GNT1, BOLA3, CDKL5, DAG1, FKRP, FKTN, GLRX5, HDAC8, ISPD, LARGE, LIAS, MECP2, NIPBL, PCDH19, PNPLA6, POMGNT1, POMT1, POMT2, RAD21, SCN1A, SEPSECS, SMC1A, SMC3, TSEN2, TSEN34, TSEN54

\*See Limitations section for information regarding areas of low coverage.

**RESULTS:**

1) Pathogenic change in Gene TSEN54  
Variant c.919G>T  
p.A307S  
Effect: Pathogenic

2) Likely Pathogenic change in Gene TSEN54  
Variant c.670\_671delAA  
p.K224fs  
Effect: Likely Pathogenic

# Benefits

This approach benefited this family in multiple aspects:

1. Provided patient with a diagnosis without a second 'stick.'
  - In general, babies don't like having their blood drawn.
2. Provided patient with a diagnosis at minimal cost.
  - Because of original gene list and tiered pricing structure, there was 'wiggle room' for the ordering physician to add on more genes without generating an additional cost to the family.
3. Provided the ordering physician with a diagnosis without having to interact with the insurance company again.
  - We all know how painful that experience can be!

## Case Example #2

23yo Female G1Po

U/S identified bilat enlarged and cystic kidneys

Seen at CNMC at 36 wk GA to discuss diagnosis, L&D plans, long-term prognosis

“At this point, the clinical picture seems consistent with autosomal recessive polycystic kidney disease.”



## Case Example #2

Baby transferred to CNMC on DOL 2

- Respiratory Distress
- Hypoglycemia
- Minor dysmorphic features noted

Molecular genetic testing for PKD1, PKD2, HNF1B, PKHD1 obtained

Baby deteriorated on DOL3, was unable to be resuscitated and expired

NBS abnl for CPTII was called out the next day

# Case Example #2

CPT2 genes were added on to sample in lab

**RESULT SUMMARY:** POSITIVE ANALYSIS. Testing identified a homozygous known pathogenic mutation in CPT2. Homozygous and compound heterozygous mutations in CPT2 have been associated with many forms of CPTII deficiency, including lethal neonatal CPTII deficiency (MIM#608836).

**CLINICAL INDICATION:** Infant male with echogenic kidneys, history of prenatal oligohydramnios, hypoglycemia, hypothermia, respiratory distress, and an abnormal nbs.

**GENES ANALYZED:** CPT2, HNF1B, PKD1\*, PKD2, PKHD1, SLC25A20 (Alias: CACT )

\*See Limitations section for information regarding areas of low coverage.

**RESULTS:**

1) Pathogenic change in Gene CPT2

Variant c.680C>T

p.P227L

Effect: Pathogenic

**INTERPRETATION:**

**Variant 1**

CPT2

c.680C>T

p.P227L

This patient is homozygous for a missense substitution in CPT2. Homozygous and compound heterozygous mutations in CPT2 have been associated with many forms of CPTII deficiency, including lethal neonatal CPTII deficiency (MIM#608836). The detected change results in a single amino acid substitution (Pro>Leu) within exon 4. There is a moderate physicochemical difference resulting from the change of this highly conserved amino acid. This alteration has been reported before in databases of affected individuals and publications as a pathogenic mutation in patients with lethal neonatal CPTII deficiency.<sup>1,2</sup> Based on the available information, this variant is pathogenic. (NM\_000098.2)

## Lethal Neonatal CPTII

Liver failure, hypoketotic **hypoglycemia**, cardiomyopathy, **respiratory distress**, and/or cardiac arrhythmias occur. Affected individuals have liver calcifications and **cystic dysplastic kidneys** [Vladutiu et al 2002b, Sigauke et al 2003].

Neuronal migration defects including cystic dysplasia of the basal ganglia have been reported [Pierce et al 1999].

Prognosis is poor. **Death occurs within days** to months.



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# Benefits

This approach benefited this family in multiple aspects:

1. Provided patient with a diagnosis at minimal cost.
  - Sample was in the lab at time of abnormal NBS result which was after patient's demise and there was no additional charge to add on the CPT2 gene.
2. Provided the family with the correct recessive disorder.
  - Recurrence risk is same for ARPKD and CPTII = 25%.
  - But with proper diagnosis and molecular confirmation, future pregnancies can be tested.
3. Quick turn-around-time of process helped ensured family was aware of the actual diagnosis.
  - Results were disclosed with genetic counseling as part of the autopsy meeting with parents.

## Case Example #3

- Newborn male born at an estimated 36-37 weeks to a G8P<sub>5</sub>→6 mom with no prenatal care.
- Apgars of 7<sup>1</sup>, 9<sup>5</sup>
- Developed respiratory distress and transferred to CNHS on an oscillator.
- Consult requested because of respiratory distress and concern for possible skeletal dysplasia
- PE: limited because of clinical state
  - Camptodactyly
  - Underrotated thumbs

# Case Example #3

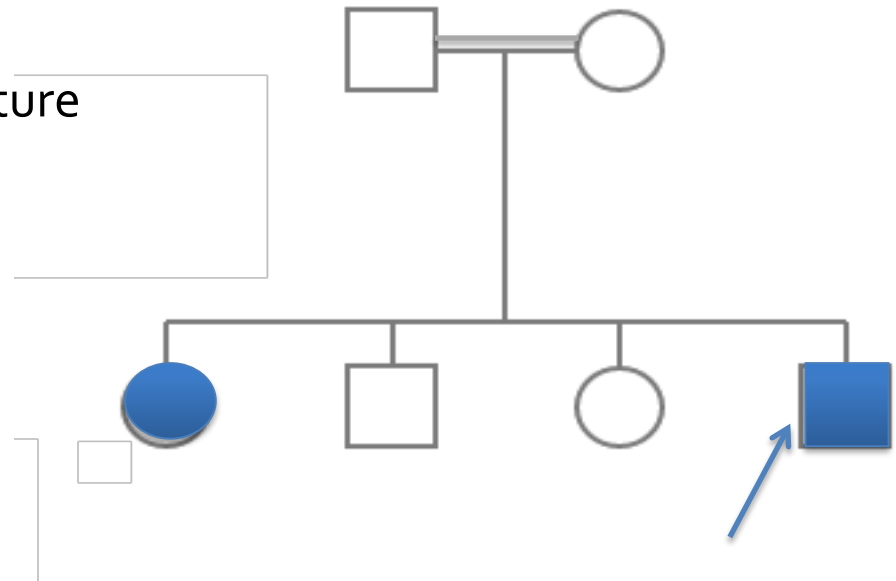
Consanguineous family

Parents: normal stature

2 siblings A&W with normal stature

12 year-old sister with

- Short stature
- Broad joints
- Hip/knee dislocations
  - Scoliosis
  - Hypodontia
- Normal intelligence
- No prior genetic workup (and no active insurance to facilitate a workup)



# CMA revealed 4.7% AOH



# Total Genes in AOH

- ▶ Add a Gene List
- ▶ Add by Phenotype
- ▶ Add by Syndrome/Genetic Disorder
- ▶ Add Genes
- ▼ Add/Remove Genes by Regions of Interest

You can filter your list to contain only those genes in Regions of Interest. Click Import to upload a file containing this data.

Browse...

Import

	Type	Call	Chr	Start	End	Length (bp)
<input checked="" type="checkbox"/>	LOH		1	147102853	150519220	3,416,367
<input checked="" type="checkbox"/>	LOH		3	80337540	90485635	10,148,095
<input checked="" type="checkbox"/>	LOH		3	93536053	104275654	10,739,601
<input checked="" type="checkbox"/>	LOH		3	112556392	118424202	5,867,810
<input checked="" type="checkbox"/>	LOH		5	31729862	46383335	14,653,473
<input checked="" type="checkbox"/>	LOH		5	49560858	68826246	19,265,388
<input checked="" type="checkbox"/>	LOH		6	11602364	38204838	26,602,474
<input checked="" type="checkbox"/>	LOH		7	38153443	45268198	7,114,755

Select All

Unselect All

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ 3.8-1.3 (Not in TrusightOne) (ROI:6:11602364-38204838)
- ☐ 3.8-1.4 (Not in TrusightOne) (ROI:6:11602364-38204838)
- ☐ 3.8-1.5 (Not in TrusightOne) (ROI:6:11602364-38204838)
- ☐ ABCB7 (ROI:X:61932503-154976950)
- ☐ ABCD1 (ROI:X:61932503-154976950)
- ☐ ABCD1P3 (Not in TrusightOne) (ROI:16:31905354-35220544)
- ☐ ABCD2 (Not in TrusightOne) (ROI:12:37857750-44359086)
- ☐ ABCF1 (Not in TrusightOne) (ROI:6:11602364-38204838)
- ☐ ABCF2P1 (Not in TrusightOne) (ROI:3:80337540-90485635)
- ☐ ABHD16A (Not in TrusightOne) (ROI:6:11602364-38204838)
- ☐ ABHD17AP1 (Not in TrusightOne) (ROI:1:147102853-150519220)
- ☐ ABHD17AP7 (Not in TrusightOne) (ROI:16:31905354-35220544)
- ☐ ABHD17AP8 (Not in TrusightOne) (ROI:16:31905354-35220544)
- ☐ ABHD17AP9 (Not in TrusightOne) (ROI:16:31905354-35220544)
- ☐ ABI3BP (ROI:3:93536053-104275654)

3896 Genes

483 Genes in TrusightOne

☐ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous



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# AR Genes in AOH

▶ Add a Gene List  
 ▶ Add by Phenotype  
 ▼ Add by Syndrome/Genetic Disorder

You can choose from the set of syndromes below. Selecting a syndrome will add the relevant genes to the panel you are ordering. You may select multiple syndromes to add to your panel

Syndrome

☐ All ☐ Autosomal Dominant ☒ Autosomal Recessive ☐ X-Linked Dominant ☐ X-Linked Recessive

202110 17,20-lyase deficiency, isolated (1 gene)  
 202110 17-alpha-hydroxylase/17,20-lyase deficiency (1 gene)  
 204750 2-aminoadipic 2-oxoadipic aciduria (1 gene)  
 610006 2-methylbutyrylglycinuria (1 gene)  
 231530 3-hydroxyacyl-CoA dehydrogenase deficiency (1 gene)  
 250620 3-hydroxyisobutyryl-CoA hydrolase deficiency (1 gene)  
 273750 3-M syndrome 1 (1 gene)  
 614205 3-M syndrome 3 (1 gene)  
 210200 3-Methylcrotonyl-CoA carboxylase 1 deficiency (1 gene)  
 210210 3-Methylcrotonyl-CoA carboxylase 2 deficiency (1 gene)  
 614739 3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like  
 250950 3-methylglutaconic aciduria, type I (1 gene)  
 258501 3-methylglutaconic aciduria, type III (1 gene)  
 610198 3-methylglutaconic aciduria, type V (1 gene)  
 257920 3MC syndrome 1 (1 gene)

Selected Genes

- ☐ **ALDH5A1** (Disease:Succinic semialdehyde dehydrogenase deficiency) (ROI:6:11602364-38204838)
- ☐ **AMACR** (Disease:Alpha-methylacyl-CoA racemase deficiency, Bile acid synthesis defect, congenital, 4) (ROI:5:31729862-46383335)
- ☐ **APOC2** (Disease:Hyperlipoproteinemia, type Ib) (ROI:19:41415817-47599748)
- ☐ **APOE** (Disease:Sea-blue histiocyte disease) (ROI:19:41415817-47599748)
- ☐ **ARFGF2** (Disease:Periventricular heterotopia with microcephaly) (ROI:20:47108341-51230686)
- ☐ **ARL6** (Disease:(Bardet-Biedl syndrome 1, modifier of)) (ROI:3:93536053-104275654)
- ☐ **ATP6AP2** (Disease:Parkinsonism with spasticity, X-linked) (ROI:X:2690826-58337890)
- ☐ **AVPR2** (Disease:Diabetes insipidus, nephrogenic) (ROI:X:61932503-154976950)
- ☐ **B3GALT1** (Disease:Peters-plus syndrome) (ROI:13:29898085-40189343)

78 Genes  
 70 Genes in TrusightOne  
☐ Only Show TrusightOne Genes

▶ Add Genes  
 ▶ Add/Remove Genes by Regions of Interest

# Clinically Relevant Genes in AOH

► Add a Gene List

▼ Add by Phenotype

You can choose from the set of phenotypes that your patient is exhibiting. Selecting from the list of phenotypes will add the relevant genes to the panel you are ordering. You may select multiple phenotypes to add to your panel

Phenotypes

- Childhood onset short-limb short stature (2 genes)
- Childhood-onset short-trunk short stature (1 gene)
- Disproportionate short stature (6 genes)
- Disproportionate short-limb short stature (23 genes)
- Disproportionate short-trunk short stature (14 genes)
- Lethal short-limbed short stature (1 gene)
- Mesomelic short stature (2 genes)
- Mild short stature (12 genes)
- Moderately short stature (3 genes)
- Neonatal short-limb short stature (9 genes)
- Neonatal short-trunk short stature (1 gene)
- Proportionate short stature (5 genes)
- Severe short stature (25 genes)
- Short stature (348 genes)**

Selected Genes

- ☐ **ERCC2** (Phenotype:Short stature)  
(Disease:Trichothiodystrophy, Xeroderma pigmentosum, group D) (ROI:19:41415817-47599748)
- ☐ **FANCE** (Phenotype:Short stature) (Disease:Fanconi anemia, complementation group E) (ROI:6:11602364-38204838)
- ☐ **GHR** (Phenotype:Short stature) (Disease:Laron dwarfism) (ROI:5:31729862-46383335)
- ☐ **LIFR** (Phenotype:Short stature) (Disease:Stuve-Wiedemann syndrome/Schwartz-Jampel type 2 syndrome) (ROI:5:31729862-46383335)
- ☐ **NEU1** (Phenotype:Short stature) (Disease:Sialidosis, type I) (ROI:6:11602364-38204838)
- ☐ **POU1F1** (Phenotype:Short stature) (Disease:Pituitary hormone deficiency, combined, 1) (ROI:3:80337540-90485635)
- ☐ **PSMB8** (Phenotype:Short stature) (Disease:Autoinflammation, lipodystrophy, and dermatosis syndrome) (ROI:6:11602364-38204838)
- ☐ **SPG20** (Phenotype:Short stature) (Disease:Troyer syndrome) (ROI:13:29898085-40189343)

13 Genes  
13 Genes in TrusightOne  
☐ Only Show TrusightOne Genes

# Recommended Testing

- *LIFR* sequencing recommended
- Result: POSITIVE

Patient is homozygous for a known pathogenic mutation in exon 8 of *LIFR*. c.756dupT, which causes a frameshift

This is consistent with a diagnosis of Stuve-Wiedemann Syndrome. This is an autosomal recessive disorder characterized by skeletal changes, bowing of the lower limbs, severe osteoporosis and joint contractures, episodic hyperthermia, respiratory insufficiency and apnea, feeding problems and high mortality in early life. Those that survive tend to have normal intelligence.

# Benefits

This approach benefited this family in multiple aspects:

1. Provided patient with a diagnosis at minimal cost.
  - Family refused to give an address; therefore, they were not eligible for Medicaid and were paying out-of-pocket for care.
2. Dictated medical care – concern for frequent respiratory events led to tracheostomy.
3. As patient's sister was without insurance, it provided her with a presumed diagnosis.
4. Quick turn-around-time of process helped family decision making (ordering of microarray to return of sequencing results was 6 weeks).

## Case Example #4

Initial visit: 6 month old male with muscle weakness, hypotonia, and bilateral ptosis.

PE: myopathic face with positional plagiocephaly. Significant motor delay (head lag). Smiles and babbles.

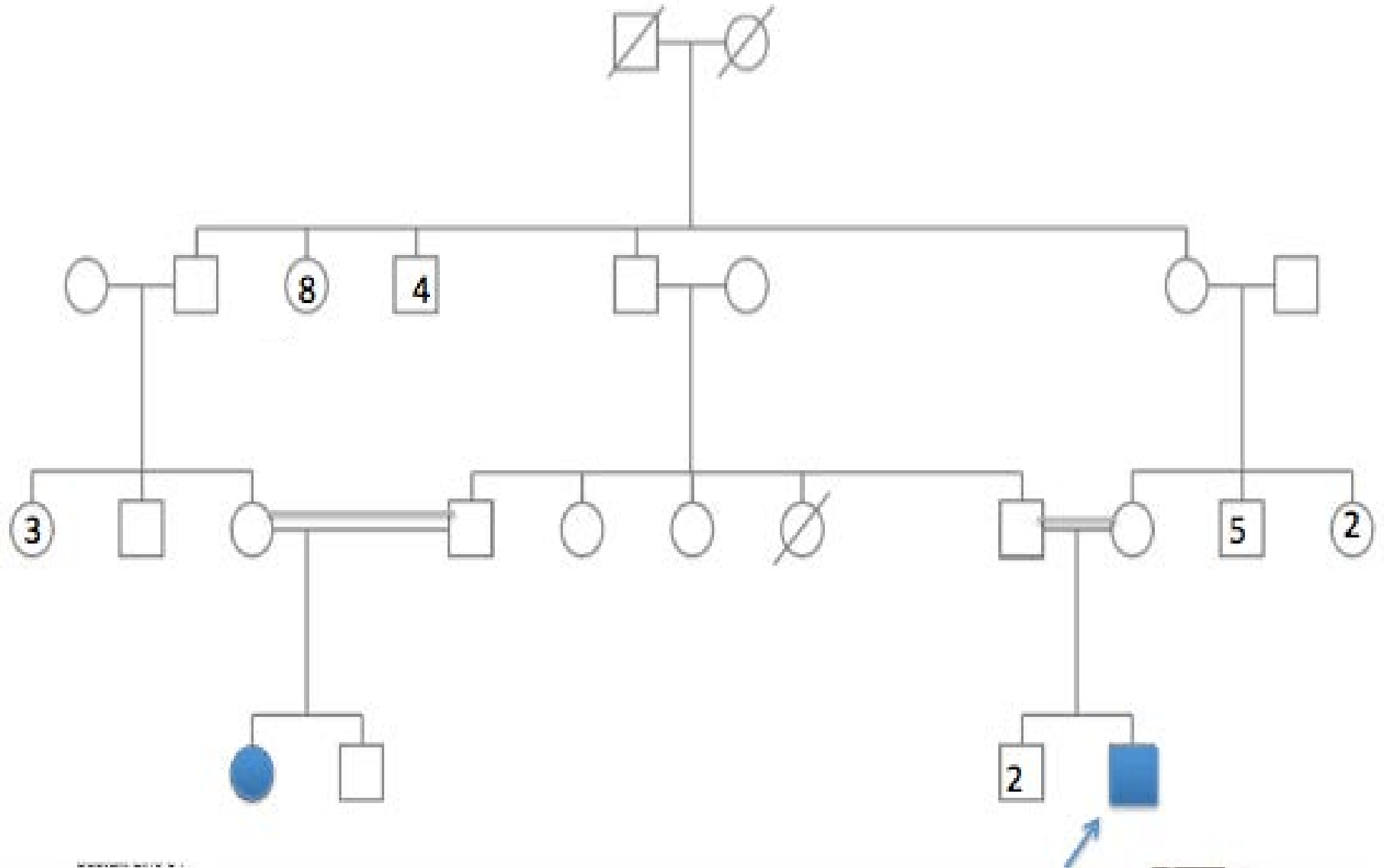
Reflexes: +1 symmetrically bilaterally on lower extremities. Unable to elicit reflexes on upper extremities.

Weight: 3<sup>rd</sup> percentile

Length: 50<sup>th</sup> percentile

HC: 10<sup>th</sup> percentile

## Case Example #4



# Case Example #4





# All Genes in AOH

- Add a Gene List
- Add by Phenotype
- Add by Syndrome/Genetic Disorder
- Add Genes
- ▼ Add/Remove Genes by Regions of Interest

You can filter your list to contain only those genes in Regions of Interest. Click Import to upload a file containing this data.

Browse...

Import

	Type	Call	Chr	Start	End	Length (bp)
<input checked="" type="checkbox"/>	LOH	Pathogenic	1	5310579	10662878	5,352,299
<input checked="" type="checkbox"/>	LOH		2	3814044	7113115	3,299,071
<input checked="" type="checkbox"/>	LOH		2	30961996	37934470	6,972,474
<input checked="" type="checkbox"/>	LOH		2	217245936	220785524	3,539,588
<input checked="" type="checkbox"/>	LOH		3	2918689	23684312	20,765,623
<input checked="" type="checkbox"/>	LOH		3	69432043	77418119	7,986,076
<input checked="" type="checkbox"/>	LOH		3	191035788	197851260	6,815,472
<input checked="" type="checkbox"/>	LOH		4	72575786	125404239	52,828,453

Select All

Unselect All

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ **AACS** (Not in TrusightOne) (ROI:12:113258057-133778166)
- ☐ **AAMP** (Not in TrusightOne) (ROI:2:217245936-220785524)
- ☐ **AARSD1** (Not in TrusightOne) (ROI:17:33797533-71736596)
- ☐ **AASS** (ROI:7:105668818-157250812)
- ☐ **AATF** (Not in TrusightOne) (ROI:17:33797533-71736596)
- ☐ **ABCA1** (ROI:9:101135200-111125929)
- ☐ **ABCA10** (ROI:17:33797533-71736596)
- ☐ **ABCA5** (Not in TrusightOne) (ROI:17:33797533-71736596)
- ☐ **ABCA6** (Not in TrusightOne) (ROI:17:33797533-71736596)
- ☐ **ABCA8** (Not in TrusightOne) (ROI:17:33797533-71736596)
- ☐ **ABCA9** (Not in TrusightOne) (ROI:17:33797533-71736596)
- ☐ **ABCB6** (ROI:2:217245936-220785524)
- ☐ **ABCB7** (ROI:X:61932503-154979182)
- ☐ **ABCB8** (Not in TrusightOne) (ROI:7:105668818-157250812)
- ☐ **ABCB9** (Not in TrusightOne) (ROI:12:113258057-133778166)

5728 Genes

762 Genes in TrusightOne

☐ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous



Children's National™

# AR genes in AOH

► Add a Gene List

► Add by Phenotype

▼ Add by Syndrome/Genetic Disorder

You can choose from the set of syndromes below. Selecting a syndrome will add the relevant genes to the panel you are ordering. You may select multiple syndromes to add to your panel

Syndrome

Filter

Reset

☐ All ☐ Autosomal Dominant ☒ Autosomal Recessive ☐ X-Linked Dominant ☐ X-Linked Recessive

202110 17,20-lyase deficiency, isolated (1 gene)  
202110 17-alpha-hydroxylase/17,20-lyase deficiency (1 gene)  
204750 2-aminoadipic 2-oxoadipic aciduria (1 gene)  
610006 2-methylbutyrylglycinuria (1 gene)  
231530 3-hydroxyacyl-CoA dehydrogenase deficiency (1 gene)  
250620 3-hydroxyisobutyryl-CoA hydrolase deficiency (1 gene)  
273750 3-M syndrome 1 (1 gene)  
614205 3-M syndrome 3 (1 gene)  
210200 3-Methylcrotonyl-CoA carboxylase 1 deficiency (1 gene)  
210210 3-Methylcrotonyl-CoA carboxylase 2 deficiency (1 gene)  
614739 3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like  
250950 3-methylglutaconic aciduria, type I (1 gene)  
258501 3-methylglutaconic aciduria, type III (1 gene)  
610198 3-methylglutaconic aciduria, type V (1 gene)  
257920 3MC syndrome 1 (1 gene)

► Add Genes

► Add/Remove Genes by Regions of Interest

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

- ☐ **AASS** (Disease:Hyperlysinemia, Saccharopinuria) (ROI:7:105668818-157250812)
- ☐ **ABCA1** (Disease:Tangier disease) (ROI:9:101135200-111125929)
- ☐ **ACACA** (Disease:Acetyl-CoA carboxylase deficiency) (ROI:17:33797533-71736596)
- ☐ **ACADS** (Disease:Acyl-CoA dehydrogenase, short-chain, deficiency of) (ROI:12:113258057-133778166)
- ☐ **ACE** (Disease:Renal tubular dysgenesis) (ROI:17:33797533-71736596)
- ☐ **ACP2** (Not in TrusightOne) (Disease:??Lysosomal acid phosphatase deficiency) (ROI:11:46891900-50200440)
- ☐ **ADAMTS17** (Disease:Weill-Marchesani-like syndrome) (ROI:15:91803213-102429049)
- ☐ **AGK** (Disease:Cataract 38, autosomal recessive, Sengers syndrome) (ROI:7:105668818-157250812)
- ☐ **AIMP1** (Disease:Leukodystrophy, hypomyelinating, 3) (ROI:4:72575786-125404239)
- ☐ **AKR1C2** (Disease:46XY sex reversal 8) (ROI:10:1789658-11355672)

173 Genes

149 Genes in TrusightOne

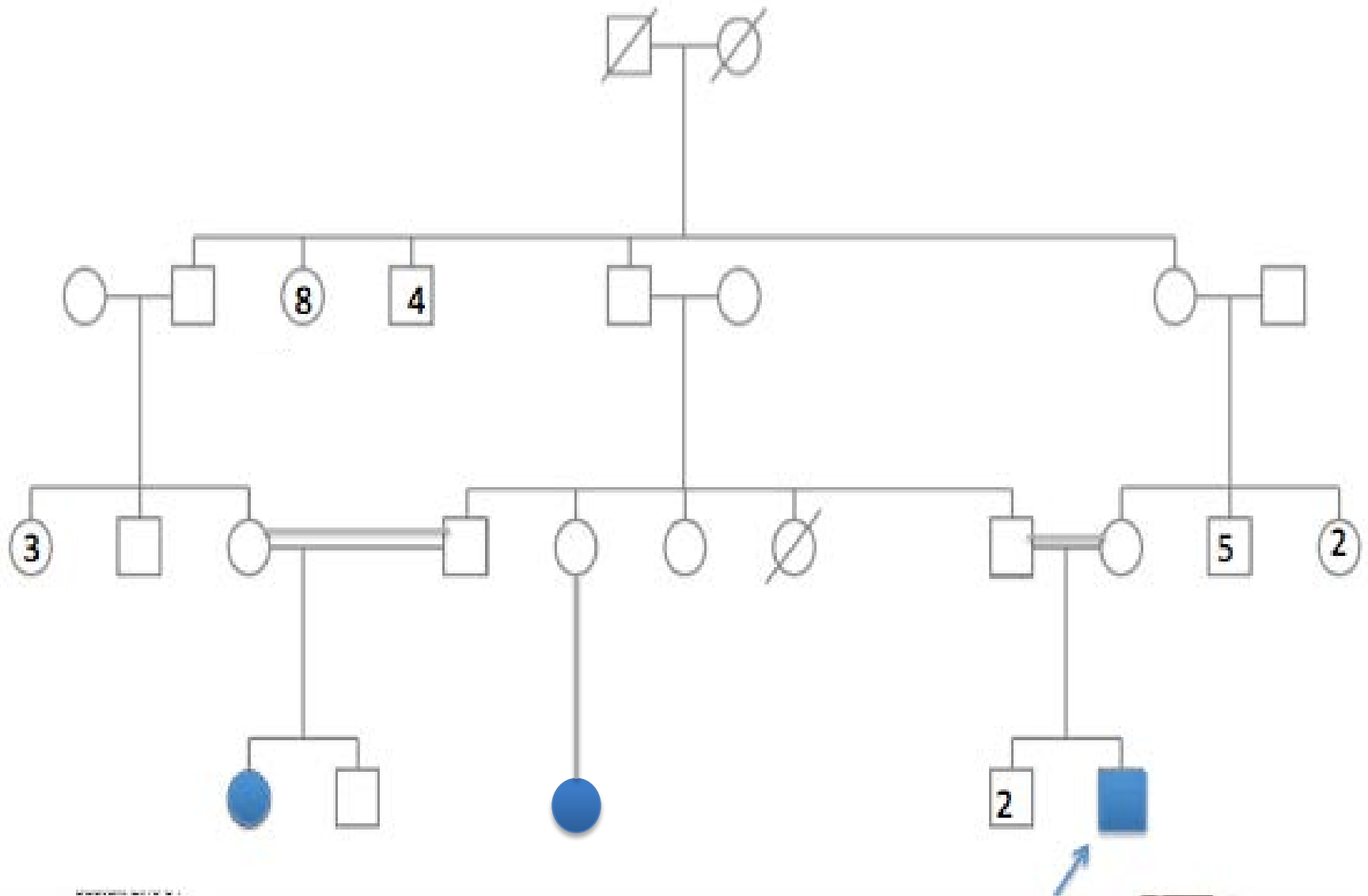
☐ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

# Surprise!



# Comparing AOH amongst cousins



# Common AR Genes

► Add a Gene List

► Add by Phenotype

► Add by Syndrome/Genetic Disorder

► Add Genes

▼ Add/Remove Genes by Regions of Interest

You can filter your list to contain only those genes in Regions of Interest. Click Import to upload a file containing this data.

Browse...

Import

	Type	Call	Chr	Start	End	Length (bp)
<input checked="" type="checkbox"/>	LOH	Pathogenic	1	5310579	10662878	5,352,299
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<input checked="" type="checkbox"/>	LOH		4	72575786	125404239	52,828,453

Select All

Unselect All

Add Genes

Remove Genes

Filter Genes

Clear Gene List

Selected Genes

☐ BTD

☒ COLQ

☐ DDB2

☒ LRP4

☒ NDUFS3

☒ RAPSQ

☐ SLC39A13

☐ WNT7A

☐ XPC

9 Genes

9 Genes in TrusightOne

☐ Only Show TrusightOne Genes

Save as Panel

Remove Selected Genes

Undo Previous

**RESULT SUMMARY:** POSITIVE ANALYSIS. Testing identified a homozygous variant in COLQ. This finding is pathogenic and consistent with a diagnosis of Endplate Acetylcholinesterase Deficiency (MIM#603034).

**CLINICAL INDICATION:** 2 year old male with hypotonia, developmental delay, and muscle weakness

**GENES ANALYZED:** COLQ, LRP4, NDUFS3, RAPSN

\*See Limitations section for information regarding areas of low coverage.

**RESULTS:**

1) Pathogenic change in Gene COLQ

Variant c.679C>T

p.R227\*

Effect: Pathogenic

**INTERPRETATION:**

**Variant 1**

COLQ

c.679C>T

p.R227\*

This patient is homozygous for nonsense substitution in COLQ. Homozygous and compound heterozygous alterations in COLQ have been associated with Endplate Acetylcholinesterase Deficiency (MIM#603034). The detected nonsense alteration in exon 12 interrupts the reading frame by introducing a premature stop codon. This alteration has been reported before in publications of individuals with Endplate Acetylcholinesterase Deficiency.<sup>1,2</sup> Based on the available information at present, this variant is pathogenic. (transcript: NM\_005677.3)

**RECOMMENDATIONS:** Clinical correlation between this result and the patient's phenotype is recommended. Genetic counseling is recommended to discuss the implications of this report.

# Homozygous *COLQ* mutation

Mutations in *COLQ* cause a type of congenital myasthenic syndrome (CMS).

Phenotype: fatigue weakness of skeletal muscle with onset at or shortly after birth (or in early childhood)

Management: most individuals with CMS benefit from acetylcholine esterase inhibitors; however, those with *COLQ* mutations can range from no response to **detrimental** effects.



# Benefits

This approach benefited this family in multiple ways:

1. Provided a presumed diagnosis for the patient's cousins.
  - Which would allow for cheaper confirmation testing – beneficial for the cousin whose insurance company had been denying genetic testing coverage.
2. Provided medical management recommendations not only for the patient, but his cousins.
3. Large, expensive genetic panels weren't necessary. All the testing was able to be completed for a lower price than the cost of most panels.

# Questions/Concerns

Kristina Cusmano-Ozog, MD, FACMG

202-476-5859

[kcozog@cnmc.org](mailto:kcozog@cnmc.org)

Sean Hofherr, PhD, FACMG

202-476-2033

[shofherr@cnmc.org](mailto:shofherr@cnmc.org)

Mary Beth Seprish, MS, CGC

202-476-4168

[mseprish@cnmc.org](mailto:mseprish@cnmc.org)