Molecular Diagnostics for Genetic Diseases

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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
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

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.
Sequencing Advancements Driving Innovation

Cost per Genome

NIH
National Human Genome Research Institute
genome.gov/sequencingcosts

Moore's Law
## Prior Options for Clinical Sequencing

<table>
<thead>
<tr>
<th>Single gene sequencing</th>
<th>Whole Exome Sequencing</th>
<th>Whole Genome Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small gene panels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large gene panels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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

- 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
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.
**ICD10 Diagnosis Code(s) Mandatory:**

**Insurane Authorization (circle one):** NOT REQUIRED or GRANTED

- **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):**
  - Anemia Panel
  - Congenital Malformation Panel
  - Developmental Delay Panel
  - DNA Extraction Panel
  - Epilepsy Panel
  - Factor V Leiden Mutation Testing
  - Fragile X Panel
  - Hypertrophic Cardiomyopathy Panel
  - Ichthyosis Panel
  - Intellectual Disability / Autism Spectrum Disorder Panel
  - Microcephaly Panel
  - Mitochondrial Disorder Panel
  - Noonan Syndrome Panel
  - Prothrombin Gene Mutation (G20210A)
  - Retinitis Pigmentosa Panel
  - THYR Panel
  - Truncal Hypoplasia Panel
  - X-linked Intellectual Disability Panel

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

**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:

- **Child's Name:**
- **Child's MRN:**

**Ethnicity (check all that apply):**

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

- ACSL4 (Phenotype: Autism)
- ADSL (Phenotype: Autism)
- AGTR2 (Phenotype: Autism)
- ALDHSA1 (Phenotype: Autism)
- ALG13 (Phenotype: Autism)
- ALMS1 (Phenotype: Autism)
- ARL8CE6 (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, heart 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
Genes associated with Speech Delay

- Delayed speech and language development (344 genes)
- 919 Genes
- 703 Genes in TrusightOne
- Only Show TrusightOne Genes

Screen showing the selection of genes associated with speech delay.
Genes associated with Motor Delay
Child w/ developmental delay AND failure to thrive
Child with developmental delay, failure to thrive AND coloboma
Child with AOH on CMA
Child with AOH on CMA
Child with AOH on CMA and a phenotype of seizures
CMA case examples
CytoScan® Dx Assay: Our 1st year experience

CMA Results
- Negative (468)
- CNV (157)
- AOH (43)

Types of CNVs Detected
- Duplication
- Deletion
- Complex
- Aneuploidy

Common CNVs Identified
- 1q21 del ASD, microcephaly 2
- 1q21 dup ASD, macrocephaly 2
- 3q13 del Primrose 1
- 5p15 del Cri du chat 1
- 5q35 del Sotos 1
- 5q35 dup Hunter McAlpine 1
- 7q11 del Williams 5
- 15q11 del PWAS 2
- 15q11 dup PWAS 2
- 16p11 dup ASD 1
- 16p13 dup CREBBP 2
- 17p11 del Smith Magenis 1
- 17p11 dup Potocki Lupski 1
- 18p11 del 18p- 1
- 18p11 trip Tetrasomy 18p 1
- 18q22 del 18q- 3
- 22q11 del VCF 6
- 22q11 dup 4
- 22q13 del Phelan McDermid 2

Inheritance of CNVs
- De novo 15
- Maternal 29
- Paternal 11

Complex CNVs Identified
- 1q44x4 Dup/Trip of 1q44
- 1q44x3
- 8p23.3p23.1x1
- 8p23.1p12x3
- 15q13.2q13.3x1 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
- Trisomy 13 1
- Trisomy 18 2
- Trisomy 21 1
- 47,XXY 2
- 47,XYY 2
- 48,XXXY 1
- Mosaic Trisomy 14 1
- Mosaic Turner 1

AOH & Identity by descent
- 1st degree relative 1
- 2nd degree relative 8
- 3rd degree relative 13
- 4th degree relative 13

AOH & UPD
- Chr 7 2
- Chr 14 4
- Chr 15 2
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
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
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, LARGE1, LIPA, MST2, NIPBL, PCDH19, PNPLA6, POMT1, RCN1, SEPTI, SMAD3, 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 G1P0
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 DOL 3, 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

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.
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 G8P5→6 mom with no prenatal care.
- Apgars of 7₁, 9₅
- 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
AR Genes in AOH
Clinically Relevant Genes in AOH
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.

Reflexes: +1 symmetrically bilaterally on lower extremities. Unable to elicit reflexes on upper extremities.
Weight: 3rd percentile
Length: 50th percentile
HC: 10th percentile
Case Example #4

11.1% AOH
### 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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Call</th>
<th>Chr</th>
<th>Start</th>
<th>End</th>
<th>Length (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOH</td>
<td>Pathogenic</td>
<td>1</td>
<td>5310579</td>
<td>10662878</td>
<td>5,352,299</td>
</tr>
<tr>
<td>LOH</td>
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<td>3814044</td>
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<td>3,299,071</td>
<td></td>
</tr>
<tr>
<td>LOH</td>
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<td>30961996</td>
<td>37934470</td>
<td>6,972,474</td>
<td></td>
</tr>
<tr>
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<td>220785524</td>
<td>3,539,588</td>
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<tr>
<td>LOH</td>
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<td>72575786</td>
<td>125404239</td>
<td>52,828,453</td>
<td></td>
</tr>
</tbody>
</table>

- **5728 Genes**
- **762 Genes in TrusightOne**
- **Only Show TrusightOne Genes**

**Selected Genes**
- AACS (Not in TrusightOne) (ROI:12:113258057-133778166)
- AAMP (Not in TrusightOne) (ROI:2:217245936-220785524)
- AARS5D1 (Not in TrusightOne) (ROI:17:33797533-71736596)
- AASS (ROI:7:105668818-157250812)
- AATF (Not in TrusightOne) (ROI:17:33797533-71736596)
- ABCA1 (ROI:9:101135200-11125929)
- 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:6:1932503-154979182)
- ABCB8 (Not in TrusightOne) (ROI:7:105668818-157250812)
- ABCB9 (Not in TrusightOne) (ROI:12:113258057-133778166)

- **Save as Panel**
- **Remove Selected Genes**
- **Undo Previous**
AR genes in AOH

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>202110</td>
<td>17,20-lyase deficiency, isolated</td>
<td>Hyperlysinemia, Saccharopinuria</td>
<td>R0:7:105668818-157250812</td>
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<tr>
<td>202110</td>
<td>17-alpha-hydroxylase/17,20-lyase deficiency</td>
<td>Tangier disease</td>
<td>R0:9:10135200-111125929</td>
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<td>204750</td>
<td>2-aminoacidic 2-oxoadipic aciduria</td>
<td>Acetyl-CoA carboxylase deficiency</td>
<td>R0:17:33787533-71735959</td>
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<tr>
<td>610006</td>
<td>2-methylbutyrlyglycinuria</td>
<td>Acyl-CoA dehydrogenase, short-chain, deficiency of</td>
<td>R0:12:113258057-133778166</td>
</tr>
<tr>
<td>231530</td>
<td>3-hydroxyacyl-CoA dehydrogenase deficiency</td>
<td>Renal tubular dysgenesis</td>
<td>R0:17:33787533-71735959</td>
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<td>250620</td>
<td>3-hydroxyisobutyryl-CoA dehydrogenase deficiency</td>
<td>Not in TrusightOne</td>
<td>R0:11:46891900-50200440</td>
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<tr>
<td>273750</td>
<td>3-M syndrome 1</td>
<td>Weill-Marchesani-like syndrome</td>
<td>R0:15:91803213-102429049</td>
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<td>614205</td>
<td>3-M syndrome 3</td>
<td>Cataract 38, autosomal recessive, Sengers syndrome</td>
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</table>

Selected Genes:

- AASS
- ABCA1
- ACACA
- ACADS
- ACE
- ACP2
- ADAMTS17
- AGK
- AIMP1
- AKR1C2

173 Genes
149 Genes in TrusightOne

Add/Remove Genes by Regions of Interest

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.

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Selected Genes
- BTD
- COLQ
- DDB2
- LRP4
- NDUFS3
- RAPSN
- SLC39A13
- WNT7A
- XPC

9 Genes
9 Genes in TrusightOne
Only Show TrusightOne Genes

Save as Panel  Remove Selected Genes  Undo Previous

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Children's National™
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.1,2 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 \textit{COLQ} mutation

Mutations in \textit{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 \textit{COLQ} mutations can range from no response to \textbf{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

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