Joint webinar series

Non-progressive congenital ataxia

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Non progressive congenital Ataxia: Webinar Outline

- Introduction and diagnostic algorithm of ataxia in children
- Definition of NPCA
- Clinical features and Examination
- Etiology
- Genetic heterogeneity
- Disease Management
- Conclusions
Learning objectives

- Recognize the presenting signs of NPCA, its co-morbidities and associated outcome
- Identify the main entities in NPCA differential diagnosis
- Assess the role of imaging in diagnosis of very early ataxias
- Identify the more common genetic etiologies of NPCA in order to guide management and genetic counseling
Q1: What is your professional background?

- Neurologist
- Pediatric neurologist
- Basic scientist
- Physiotherapist
- Nurse
- Other
Ataxia in children: classification

- Acute (acquired)
- Recurrent
- Progressive
- Non-progressive, congenital

  - Cerebellar
  - Sensory
  - Vestibular
Non-progressive ataxia

Trio-based WES: candidate gene
No matches on MME
NBIA gene screen: (-)
Clinical diagnostic algorithm in early-onset ataxia

Step 1
- Cerebellar ataxia?
  - Exclude ataxia mimics
  - Exclude acquired ataxia

Step 2
- In EOAt, consider assessment of:
  - Inventory of Non-Ataxic Symptoms (INAS)
  - Quantification of ataxia (SARA)
  - Eye movements

Step 3
- Family history or distinct phenotype? ^+
  - Yes
    - Direct testing of gene mutation
      - Consider repeat disorders
  - No
    - Step 4

Step 4
- Perform brain MRI
  - Specific hindbrain abnormalities
  - No MRI abnormalities
    - Other abnormalities *%
      - Specific hindbrain abnormalities
  - No diagnosis
    - Consider inclusion in ataxia database

Step 5
- Perform laboratory investigations^5
  - Perform specific gene panel*

Step 6
- Consider Array Investigation

Step 7
- NGS techniques*%
  - No diagnosis

Brandsma R et al., EJPN 2019
Q2: Which among the following is not a hindbrain anomaly associated with early-onset ataxia?

A. Dragonfly pattern
B. Molar tooth sign
C. Hypoplastic vermis + enlarged posterior fossa
D. Blake pouch’s cyst
Imaging in childhood Genetic Ataxia: rhombencephalalic abnormal patterns

Clinical diagnostic algorithm in early-onset ataxia

Brandsma R et al., EJPN 2019
SARA scale in children

From Lawerman TF et al., Dev Med Child Neurol, 2017

Brandsma R et al., DMCN 2014

Lawerman TF et al., DMCN 2017

Lawerman TF et al., DMCN 2017

Brandsma R et al., DMCN 2014
Non-Progressive Congenital Ataxia (NPCA)

- Children with early evidence of cerebellar ataxia, without progression on follow-up, and even the tendency to gradual improvement
- Excluded:
  - Lesions following prenatal infection, perinatal illness, supratentorial brain malformations, defined syndromal disorders associated with ataxia, and postnatally acquired neurologic diseases
  - Hindbrain malformations with recognizable neuroradiological pattern

Steinlin, Zangger & Boltshauser, DMCN 1998
Bertini, Zanni & Boltshauser, Hand Clin Neurol 2018
NPCA: History

• Batten FE: “Ataxia in childhood” (Brain, 1905)

• Norman RM: “Primary degeneration of the granular layer of the cerebellum” (Brain, 1940)

• Steinlin, Zangger & Boltshauser: “Non-progressive congenital ataxia” (DMCN, 1998)
NPCA or "Ataxic CP"

Early ataxic motor disorder
No regression
Absence of perinatal injury

De novo point mutations in patients diagnosed with ataxic cerebral palsy

Ricardo Parolin Schnekenberg, Emma M. Perkins, Jack W. Miller, Wayne I. L. Davies, Maria Cristina D'Adamo, Mauro Pessa, Katherine A. Fawcett, David Sims, Elodie Gillard, Karl Hudspith, Paul Skehel, Jonathan Williams, Mary O'Regan, Sandeep Jayawant, Rosalind Jefferson, Sarah Hughes, Andrea Lustenberger, Jiannis Ragoussis, Mandy Jackson, Stephen J. Tucker and Andrea H. Németh
Q3: Which of the following is true about NPCA clinical features

A. Seizures are rare in NPCA
B. Most patients walk unassisted before age 10
C. Oculomotor anomalies are a late clinical sign
D. Normal cognition occurs in more than 50%
NPCA: early signs

- Infantile hypotonia
- Motor delay
- Speech delay
- Ocular dyspraxia / nystagmus
NPCA: clinical features in children and adults

- High prevalence of cognitive and language impairments
- Increased occurrence of seizures
- Ocular signs (nystagmus, strabismus)
- Behavioral disorders
- Microcephaly
- Spasticity
- Dystonia
Other congenital ataxic syndromes

- Cerebellar – destructive lesions
- Progressive cerebellar with onset in infancy
- Sensory ataxia
- Leukoencephalopathy
Congenital ataxia: genetic vs. acquired

A.J. - PT 27wk, ID
J.S. - PT 24wk, ID, ASD, ocular dysp.
E.C. - PT 24wk, mild ID
I.R. - PT 26 wk, mild ID, ataxia
Some progressive ataxias with infantile onset

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mode of Inheritance</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Ataxia-telangiectasia</td>
<td>AR</td>
<td>ATM</td>
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<tr>
<td>Ataxia-telangiectasia–like disorder 2</td>
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<td>PCNA</td>
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<td>Spastic Ataxia 6</td>
<td>AR</td>
<td>SACS</td>
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<td>SCAR 12</td>
<td>AR</td>
<td>WWOX</td>
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<td>SCAR 13</td>
<td>AR</td>
<td>GRM1</td>
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<td>AR</td>
<td>KIAA0226</td>
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<td>SCAR 20</td>
<td>AR</td>
<td>SNX14</td>
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<td>Succinyl semialdehyde DH deficiency</td>
<td>AR</td>
<td>ALDH5A1</td>
</tr>
<tr>
<td>Marinesco-Sjögren syndrome</td>
<td>AR</td>
<td>SIL1</td>
</tr>
<tr>
<td>SCA 13</td>
<td>AD</td>
<td>KCNC3</td>
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</tbody>
</table>

Difficult distinction among NPCA and very early-onset slowly progressive ataxia in young children

Congenital Sensory Ataxia:

**PIEZO 2 biallelic mutations:**

- Non-selective cation channel
- Mechanically activated – currents in somatosensory neurons
- Loss of proprioception and discriminative touch
- Ataxia, dysmetria, scoliosis

Chesler AT et al, 2016

The Role of PIEZO2 in Human Mechanosensation
Chesler AT et al, 2016
Congenital ataxia: Leukoencephalopathy

**GJC2 biallelic variants**

GAP junction protein (Connexin 47)
Hypomyelinating leukoencephalopathy -2

Occasional, mild cerebellar atrophy

Ataxia may precede and overshadow spasticity
Non-Progressive Congenital Ataxia (NPCA): Imaging

- Normal findings
- Cerebellar hypoplasia - vermis/hemispheres
- Prominent interfolial spaces (atrophy vs. underdevelopment)
Q4: What is the most common genetic cause of congenital ataxia?

A. De novo heterozygous mutations
B. Microdeletions
C. Autosomal dominant inheritance
D. Autosomal recessive inheritance
## Genetic basis of NPCA

### Summary of autosomal genes associated with nonprogressive congenital ataxia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Cytogenetic band</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CACNA1A</strong></td>
<td>Congenital or early-onset ataxia, ± hemiplegic migraine, ± seizures</td>
<td>19p13.13</td>
<td>Blumkin et al. (2010)</td>
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<tr>
<td><strong>KCNJ3</strong></td>
<td>Ataxia, ID, seizures, short stature</td>
<td>19q13.33</td>
<td>Travaglini et al. (2017)</td>
</tr>
<tr>
<td><strong>ITPR1</strong></td>
<td>Ataxia, ± ID, ± aniridia (Gillespie syndrome)</td>
<td>3p26.1</td>
<td>Figueroa et al. (2010)</td>
</tr>
<tr>
<td><strong>VLDLR</strong></td>
<td>Ataxia, ID, ± short stature, ± pachygyria</td>
<td>9p24.2</td>
<td>Huang et al. (2012)</td>
</tr>
<tr>
<td><strong>WDR81</strong></td>
<td>Ataxia, ID, pyramidal signs, cerebral atrophy</td>
<td>17p13.3</td>
<td>McEntagert et al. (2016)</td>
</tr>
<tr>
<td><strong>CA8</strong></td>
<td>Ataxia, mild ID</td>
<td>8q12.1</td>
<td>Boycott et al. (2005)</td>
</tr>
<tr>
<td><strong>ATP8A2</strong></td>
<td>Ataxia, severe ID, cortical atrophy</td>
<td>13q12.1</td>
<td>Gulsuner et al. (2011)</td>
</tr>
<tr>
<td><strong>PMP2LA</strong></td>
<td>Ataxia, ID, short stature</td>
<td>9q34.3</td>
<td>Turkmen et al. (2009)</td>
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<tr>
<td><strong>WVOOX</strong></td>
<td>Ataxia, ID, seizures, limb spasticity</td>
<td>16q23.1</td>
<td>Onat et al. (2013)</td>
</tr>
<tr>
<td><strong>GRM1</strong></td>
<td>Ataxia, ID, pyramidal signs, seizures, short stature</td>
<td>6q24.3</td>
<td>Choquet et al. (2016)</td>
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<tr>
<td><strong>SPTBN2</strong></td>
<td>Ataxia, ID, eye movement abnormalities</td>
<td>11q13.2</td>
<td>Gribaa et al. (2007)</td>
</tr>
<tr>
<td><strong>KCNJ10</strong></td>
<td>EAST syndrome</td>
<td>1q23.2</td>
<td>Guerguelcheva et al. (2012)</td>
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<tr>
<td><strong>KIAA0226</strong></td>
<td>Nonsyndromic early-onset ataxia</td>
<td>3q29</td>
<td>Lise et al. (2012)</td>
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<tr>
<td><strong>GRID2</strong></td>
<td>Early-onset ataxia, ID, eye movement abnormalities</td>
<td>4q22.1</td>
<td>Scholl et al. (2009)</td>
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<tr>
<td><strong>WDR73</strong></td>
<td>Ataxia, microcephaly, ID, short stature, optic atrophy</td>
<td>15q25.2</td>
<td>Nicita et al. (2017)</td>
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<tr>
<td><strong>CAMTA1</strong></td>
<td>Early-onset ataxia, mild ID, ± seizures</td>
<td>1p36.31</td>
<td>Assoum et al. (2010)</td>
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<tr>
<td><strong>ATCAY</strong></td>
<td>Ataxia, ID, tremor</td>
<td>19p13.3</td>
<td>Hills et al. (2013)</td>
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<tr>
<td><strong>ATG5</strong></td>
<td>Ataxia, ID</td>
<td>6q21</td>
<td>Vodopiatz et al. (2015)</td>
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</tbody>
</table>

EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; ID, intellectual disability.

Genetic basis of NPCA
<table>
<thead>
<tr>
<th>GO biological process</th>
<th>Fold</th>
<th>pvalue</th>
<th>Genes</th>
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</thead>
<tbody>
<tr>
<td>Rhythmic synaptic transmission</td>
<td>&gt; 100</td>
<td>6.29E-05</td>
<td>CACNA2D2, CACNA1A</td>
</tr>
<tr>
<td>Negative regulation of histone H4 acetylation</td>
<td>&gt; 100</td>
<td>6.29E-05</td>
<td>ATG5, CTBP1</td>
</tr>
<tr>
<td>Aggrephagy</td>
<td>&gt; 100</td>
<td>8.38E-05</td>
<td>ATG5, WDR81</td>
</tr>
<tr>
<td>Cerebellar Purkinje cell layer morphogenesis</td>
<td>&gt; 100</td>
<td>4.76E-06</td>
<td>SPTBN2, CACNA1A, SKOR2</td>
</tr>
<tr>
<td>Cell differentiation in hindbrain</td>
<td>77.38</td>
<td>1.12E-05</td>
<td>GRID2, CACNA1A, SKOR2</td>
</tr>
<tr>
<td>Cerebellar cortex formation</td>
<td>70.93</td>
<td>1.42E-05</td>
<td>GRID2, CACNA1A, SKOR2</td>
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</tbody>
</table>
Patient sample

• 21 subjects evaluated for suspected cerebellar syndrome in infancy, evolving into overt ataxia on follow-up
• 2 excluded after diagnosis of non-cerebellar conditions
• Negative family history
• Normal or unspecific findings on neuroimaging at presentation (MTM, PF cysts, RES, PCH pattern excluded)
• Negative “standard” work-up (CDG, other metabolic screen, lactate, vit E, Ig’s)
• Non-progressive course

• All cases underwent WES analysis: Trio (14) or Singleton (7) between 2012 and 2018
## Patients: clinical presentation

<table>
<thead>
<tr>
<th></th>
<th>Gene</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Initial symptoms</th>
<th>Initial MRI (age)</th>
<th>Independent gait (age)</th>
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<tr>
<td>1</td>
<td>Candidate</td>
<td>M</td>
<td>19</td>
<td>Motor developmental delay</td>
<td>Normal (22 mo)</td>
<td>5 y</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>F</td>
<td>24</td>
<td>Motor and speech delay</td>
<td>Vermian hypoplasia (19 mo)</td>
<td>9 y</td>
</tr>
<tr>
<td>3</td>
<td>ITPR1</td>
<td>M</td>
<td>17</td>
<td>Hypotonia, head lag, “mydriasis”</td>
<td>Global CA (23 mo)</td>
<td>3 y</td>
</tr>
<tr>
<td>4</td>
<td>CACNA1A</td>
<td>M</td>
<td>9</td>
<td>Hypotonia, abn.ocular movements</td>
<td>Normal (13 mo)</td>
<td>Non-ambulatory</td>
</tr>
<tr>
<td>5</td>
<td>SLC39A8</td>
<td>F</td>
<td>19</td>
<td>Hypotonia, GDD, ocular dyspraxia</td>
<td>Global CA (9 mo)</td>
<td>Few steps unsupported</td>
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<tr>
<td>6</td>
<td>STXBP1</td>
<td>M</td>
<td>10</td>
<td>Hypotonia, titubation</td>
<td>Mild vermillion atrophy (2y)</td>
<td>2 y</td>
</tr>
<tr>
<td>7</td>
<td>CA8</td>
<td>M</td>
<td>7</td>
<td>Hypotonia, motor delay</td>
<td>Mild vermillion atrophy (2y)</td>
<td>6 y</td>
</tr>
<tr>
<td>8</td>
<td>CTBP1</td>
<td>M</td>
<td>11</td>
<td>Motor and language delay</td>
<td>Mild CA (22 mo)</td>
<td>Non-ambulatory</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>M</td>
<td>10</td>
<td>Hypotonia, motor delay</td>
<td>Normal (4y)</td>
<td>2 y</td>
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<tr>
<td>10</td>
<td>Candidate</td>
<td>M</td>
<td>14</td>
<td>Hypotonia, motor delay</td>
<td>Normal (3y)</td>
<td>3,5 y</td>
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<tr>
<td>11</td>
<td>ITPR1</td>
<td>M</td>
<td>6</td>
<td>Hypotonia, poor visual tracking</td>
<td>Normal (5 mo)</td>
<td>Non-ambulatory</td>
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<td>12</td>
<td>ALDH5A1</td>
<td>M</td>
<td>12</td>
<td>Hypotonia, motor delay, absent speech</td>
<td>Normal (1 mo)</td>
<td>4 y</td>
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<tr>
<td>13</td>
<td>-</td>
<td>F</td>
<td>6</td>
<td>Motor delay</td>
<td>Normal (23 mo)</td>
<td>2 y</td>
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<tr>
<td>14</td>
<td>SLC2A1</td>
<td>M</td>
<td>5</td>
<td>Motor delay</td>
<td>Normal (19 mo)</td>
<td>2 y</td>
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<td>15</td>
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<td>F</td>
<td>13</td>
<td>GDD</td>
<td>Normal (8 y)</td>
<td>2 y</td>
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<tr>
<td>16</td>
<td>EBF3</td>
<td>M</td>
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<td>Motor delay, ocular dyspraxia</td>
<td>Vermian hypoplasia (18 mo)</td>
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<td>PPP2R5D</td>
<td>F</td>
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<td>Hypotonia, GDD, ocular dyspraxia</td>
<td>Normal (2 y)</td>
<td>3 y</td>
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<tr>
<td>18</td>
<td>-</td>
<td>F</td>
<td>13</td>
<td>Hypotonia, GDD</td>
<td>Normal (2 y)</td>
<td>2 y</td>
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<tr>
<td>19</td>
<td>-</td>
<td>F</td>
<td>7</td>
<td>Hypotonia, GDD, ocular apraxia,apnea</td>
<td>Normal (1 mo)</td>
<td>4 y</td>
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<td>Pt</td>
<td>Gene</td>
<td>Cognitive dysfunction</td>
<td>Seizures</td>
<td>Spasticity</td>
<td>Oculomotor</td>
<td>Other</td>
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<td>No</td>
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<td>nystagmus</td>
<td>Dystonia</td>
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<td>2</td>
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<td>No</td>
<td>-</td>
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<tr>
<td>3</td>
<td>ITPR1</td>
<td>Moderate</td>
<td>No</td>
<td>↑DTRs</td>
<td>OMA, hypometric saccades</td>
<td>Iris hypoplasia</td>
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<td>Dyspraxia</td>
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<td>↑DTRs</td>
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<td>Consanguinity</td>
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<td>↑DTRs</td>
<td>Saccadization</td>
<td>Consanguinity</td>
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<td>No</td>
<td>Square jerks</td>
<td>Scoliosis, vitiligo</td>
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<td>-</td>
<td>Mild</td>
<td>No</td>
<td>↑DTRs</td>
<td>Dyspraxia</td>
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<td>Candidate</td>
<td>Mild</td>
<td>No</td>
<td>No</td>
<td>Dyspraxia</td>
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<td>ITPR1</td>
<td>Mild</td>
<td>No</td>
<td>↑DTRs</td>
<td>Nystagmus</td>
<td>“Arreactive mydriasis”</td>
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<td>12</td>
<td>ALDH5A1</td>
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<td>Hypomimia</td>
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<td>-</td>
<td>Moderate</td>
<td>Yes?</td>
<td>Brisk DTRs</td>
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<td>Hypoglycorrhachia</td>
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<td>SLC2A1</td>
<td>Mild</td>
<td>No</td>
<td>↑DTRs</td>
<td>-</td>
<td>ADHD</td>
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<td>Learning dis.</td>
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<td>Yes</td>
<td>-</td>
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<td>16</td>
<td>EBF3</td>
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<td>No</td>
<td>Nystagmus, dyspraxia</td>
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<td>No</td>
<td>-</td>
<td>Macrocephaly Enamel dysplasia</td>
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<td>18</td>
<td>-</td>
<td>Moderate</td>
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<td>No</td>
<td>Scoliosis, vertebral fusion</td>
<td>Mild CA, stable</td>
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<tr>
<td>19</td>
<td>-</td>
<td>Severe</td>
<td>No</td>
<td>No</td>
<td>apraxia</td>
<td>Hypomimia, ASD</td>
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</table>
Trio-based WES in Developmental Encephalopathies
NPCA -- Ataxia/ID/ASD/Epilepsy

WES 21 cases

- DIAGNOSIS (known genes) 11/19 (58%)
- "NEGATIVE" 5/19 (26%)
- CANDIDATE 3/19 (16%)

2 excluded Non-NPCA

3 AR
8 AD
Developmental disorders with NPCA as leading clinical sign
**CACNA1A**: One gene, many phenotypes

$\alpha_1$ subunit of voltage-gated neuronal calcium P/Q channel

Spinocerebellar ataxia (SCA6)

Normal: $\text{(CAG)}_{4-18}$

Mutant: $\text{(CAG)}_{21-33}$

(polyglutamine tract)

Familial Hemiplegic Migraine

Episodic Ataxia type-2

EIEE 42

GoF

LoF

Biallelic
Congenital ataxia: \textit{CACNA1A} encephalopathy

Urgaze tonic deviation
Congenital ataxia: CACNA1A encephalopathy

Non-progressive ataxia despite increasing CA
Seizures and coma episodes after minor head trauma
No improvement on acetazolamide

Bahamonde MI et al., 2015
Congenital ataxia: \textit{ITPR1}

Schnekenberg et al. Brain 2015

Hall HN et al., Human Genetics (2019)
Cerebellar ataxia, mental retardation and dysequilibrium syndromes (CAMRQs)

WES reanalysis: RoH

NM_004056 chr8: 61144941; CA8 c.418-3C>G Hom pLI = 0.78

Trio analysis of new candidate genes:
Rule out homozygous even if non-consanguineous (RoH)
Consider low/moderate effect variants
Dysequilibrium (CAMRQ) syndromes:

Type 1: *VLDLR*
Type 2: *WDR81*
Type 3: *CA8*
NPCA as part of complex neurodevelopmental disorders
Congenital ataxia: STXBP1

NPCA; Seizure onset: age 4 y

The STXBP1-related phenotypes:

- EIEE (Ohtahara’s)
- ID, ASD
Congenital ataxia: *de novo* *EBF3* variant

De novo variants in *EBF3* are associated with hypotonia, developmental delay, intellectual disability, and autism

Tanaka AJ et al., 2017

**EFBN1** haploinsufficiency:

- Hypotonia
- Developmental delay
- ID, autism
- Facial dysmorphism
  * Ataxia 6/7
- Oculomotor apraxia
Congenital ataxia: **PPP2R5D**

*De Novo Missense Variants in PPP2R5D Are Associated with Intellectual Disability, Macrocephaly, Hypotonia, and Autism*

Linshan Shang¹, Lindsay B. Henderson², Megan T. Cho², Donald S. Petrey³, Chin-To Fong⁴, Katrina M. Haude⁴, Natasha Shur⁵, Julie Lundberg⁵, Natalie Hauser⁵, Jason Carmichael⁶, Jeffrey Innis⁷, Jane Schuette⁷, Yvonne W. Wu⁹, Shailesh Asaikar¹⁰, Margaret Pearson¹¹, Leandra Folk², Kyle Retterer², Kristin G. Monaghan², and Wendy K. Chung¹,¹²,*

- ASD, ID gene
- Regulates PI3K/AKT and tau phosphorylation
- 2/7 Ataxia
A recurrent de novo CTBP1 mutation is associated with developmental delay, hypotonia, ataxia, and tooth enamel defects
Metabolic disorders presenting as NPCA
Congenital ataxia: *ALDH5A1*

- **Succinic Semialdehyde Dehydrogenase Deficiency**
- Static encephalopathy characterized by:
  - Cognitive deficiency
  - Prominent expressive language deficit
  - Hypotonia
  - Epilepsy
  - Hyporeflexia
  - Ataxia
- Increased urine gamma OH butyrate

At age 2 y: “dysequilibrium”, global delay
Complete ataxic syndrome
Severe dysphasia
Upbeat nystagmus on vertical gaze
Congenital ataxia: SLC39A8

Autosomal-Recessive Intellectual Disability with Cerebellar Atrophy Syndrome Caused by Mutation of the Manganese and Zinc Transporter Gene SLC39A8

Kym M. Boycott,1,15* Chandree L. Beaulieu,1,15 Kristin D. Kernohan,1 Ola H. Gebril,2 Aziz Mhanni,3

Mn, Zn, other cofactors deficiency
Hutterite, Egyptian population
Hypotonia – squint - ID – short stature
Cerebellar atrophy
Type II In CDG
Leigh-like syndrome
Therapy in NPCA

• Physical – occupational therapy

• **CACNA1A:**
  – Combined corticosteroid pulses and hypertonic solution in acute decompensations *(Camia F et al Cephalalgia 2017)*
  – Acetazolamide

• SSADH deficiency:
  – Vigabatrin
Key Points / Conclusions

• Early-onset of clinical signs (1st year), more often hypotonia and motor delay

• Global developmental delay and abnormal ocular movements common

• Ataxia is essentially non-progressive, but seizures, cognitive and behavioural impairment common (overlap with other developmental encephalopathies)

• Imaging ranges from normal to isolated cerebellar atrophy/hypoplasia

• Over 35 associated genes, increasing heterogeneity

• Previously considered to fall into AR-IOSCA category, but distinct genetic counseling and prognosis