Clinical trial readiness for syndromic neurodevelopmental disorders

Tarjan Lecture Series
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Editor-in-Chief of AAN Continuum Child Neurology Edition

Speakers Bureau for Medical Education Network
Talk outline

• Overview of syndromic neurodevelopmental disorders

• Clinical trial readiness – concepts and data

• Next steps
Advances in methods to examine ASD genetics

Karyotyping and FISH (Florescent in situ Hybridization)
3-5 million BPs

Chromosomal Microarray
100 Kb

Whole exome and genome sequencing
Analysis at the level of single base pair

Ramaswami, 2018
Recommended testing

Genetic testing is the only *routinely* recommended medical workup for individuals with ASD

- Chromosomal microarray
- Boys: Fragile X
- Girls: MECP2 testing

*(Whole exome sequencing if CMA is negative)*

Schaefer et al, 2013
Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders

Siddharth Srivastava, MD,1 Jamie A. Love-Nichols, MS, MPH,1 Kiran A. Dies, ScM1
David H. Ledbetter, PhD2, Christa L. Martin, PhD1, Wendy K. Chung, MD, PhD1,3,4
Helen V. Firth, DM, FRCP2, Thomas Frazier, PhD2, Robin L. Hansen, MD2, Lisa Prock, MD, MPH1,3,9
Han Brunner, MD10,11,12, Ny Hoang, MS13,14,15, Stephen W. Scherer, PhD14,15,16,17, and the NDD Exome Scoping Review Work Group

Srivastava et al, 2019
Continued issues:

• Access and cost of testing
• Genetic counseling and clinical follow up

Srivastava et al, 2019
>30% of ID/ASD have an identified genetic cause

“Isn’t genetic testing just academic?”

“How will this testing help my child/family?”
• Community building

• Clinical monitoring and surveillance of comorbidities

• Potential for targeted therapeutics and clinical trials
• Community building

• Clinical monitoring and surveillance of comorbidities

• Potential for targeted therapeutics and clinical trials
ROLE OF PAG’s

- Family support
- Clinical and research resources
- Advocacy
- Facilitation of clinical care
- Facilitation of research:
  - Patient registries
  - Biorepositories
  - Clinical trials
PAG involvement

• 76% of families (n=28) reported PAG participation

• Of those participating in a PAG, 68% indicated that they had confidence in how to proceed with next steps in care for their child.

• In contrast, 44% of families who were not members of a PAG indicated confidence in next steps.

• Greatest participation in PAG’s in parents of children < age 3 (100%)

Simon et al, in prep
• Community building

• Clinical monitoring and surveillance of comorbidities

• Potential for targeted therapeutics and clinical trials
Clinical features in syndromic NDDs guide monitoring

*Not simply autism spectrum disorder...*

- Global developmental delay (esp motor delays, hypotonia)
- Intellectual disability
- Epilepsy and other neurological comorbidities
- Other system involvement (cardiac, endocrine, dermatologic)

Tammimies, 2015; Bishop et al, 2017; Fernandez, 2017; Bakke et al, 2018
UCLA CARING clinic (Care and research in neurogenetics)

INTAKE and TRIAGE
- History
- Prior records
- Diagnostic journey

Genetics

Psychiatry

Psychology

Neurology

Research

CARING database

BBIGS
Brain & Behavior in Genetic Syndromes

Comprehensive After Visit Summary
• Community building

• Clinical monitoring and surveillance of comorbidities

• Potential for targeted therapeutics and clinical trials
A goal of precision health – syndrome specific treatments
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Medications

Gene Editing (CRISPR)

ASOs
Antisense oligonucleotides (ASOs) are short chemically-modified strands of nucleotides.
Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy


10000+ children and adults with spinal muscular atrophy (SMA) have been treated with SPINRAZA worldwide.†

†Based on commercial patients, early access patients, and clinical trial participants as of December 2019.
Takeda and Ovid Therapeutics Expand Clinical Program for TAK-935/OV935 with Three New Studies in Rare Developmental and Epileptic Encephalopathies (DEE)

July 18, 2018 | Osaka, Japan and New York, NY

Roche, Biogen and Ionis Announce Collaborative Research Partnership

Aug 14, 2019 | PDF Version

Ultragenyx Announces Partnership with GeneTx to Advance Treatment for Angelman Syndrome

Program aims to be first disease-modifying treatment for this serious neurogenetic disorder

NNZ-2591 FOR PHELAN-MCDERMID, ANGELMAN AND PITT HOPKINS SYNDROMES

Study BP40654
Angelman Syndrome Endpoint Study
Major challenges in clinical trial success

(1) Standardized clinical measures do not adequately capture function or change

(2) Difficult to know if the drug has “hit the target”

(3) These syndromes are RARE and geographically dispersed.
Goals for clinical trial readiness...

- **Determine the most meaningful and measurable clinical endpoints**

- **Identify mechanistic biomarkers that can inform drug target engagement (and perhaps patient selection)**

- **Design protocols and develop methods that maximize access and scalability**
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**Dup15q syndrome**

Maternally derived duplications of 15q11.2-q13.1 region are one of the most frequently reported chromosomal abnormalities in ASD.

- Hypotonia (90%)
- Global developmental delay (80%)
- Autism Spectrum Disorder (50-80%)
- Epilepsy (50%)

References:
- Al Ageeli, 2014; Urraca, 2013; Hogart, 2010; Battaglia, 2010; Conant, 2014; Finucane, 2016, Distefano, 2016;
- Urraca et al, 2018; Distefano et al, 2020
Family meetings
Orlando 2015
Redondo Beach 2017
Houston 2019

62 children ages 2.5-18
Developmental domains to assess

• Cognition

• Motor skills

• Adaptive skills

• Social skills
Identification of a distinct developmental and behavioral profile in children with Dup15q syndrome

Distefano et al., JNDD 2016
Autism Spectrum Disorder, Intellectual Disability, and Delayed Walking

Somer L. Bishop, PhD, Audrey Thurm, PhD, Cristan Farmer, PhD, Catherine Lord, PhD

Bishop et al, 2016, 2017
Standardized questionnaires are problematic in severe ID

- **Social Responsiveness Scale** *(Constantino, 2003)*
  “Gives unusual or illogical reasons for doing things”
  “Is aware of what others are thinking or feeling”

- **Child Behavior Checklist** *(Achenbach, 2001)*
  - “Can’t get his/her mind of certain thoughts”
  - “Feels or complains that no one loves him/her”

Quantitative Gait Analysis in Duplication 15q Syndrome and Nonsyndromic ASD

Rujuta B. Wilson, David Elashoff, Arnaud Goselle, Beth A. Smith, Andrew M. Wilson, Abigail Dickinson, Tabitha Safat, Carly Hyde, and Shafali S. Jeste

Wilson et al., Autism Research 2020
• **Determine the most meaningful and measurable clinical endpoints**

Adaptive skills interview provides more stratification

Ratio IQ scores may prevent clustering at the “floor”

Need to measure motor skills – quantitative tools can be used

Individuals with epilepsy overall have more developmental challenges
Goals for clinical trial readiness...

• *Determine the most meaningful and measurable* clinical endpoints

• *Identify mechanistic biomarkers* that can inform drug target engagement (and perhaps patient selection)

• *Design protocols and develop methods* that maximize access and scalability
“Characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions”

Robb and McInnes, *JAMA*, 2016; FDA-NIH Biomarker Working Group, 2016
Dup15q syndrome
• Initial acclimation
  • explore room, favorite movie playing, reinforcers, rapport building

• Netting
  • training net, modeled by parent, incremental practice with reinforcers, favorite move playing

• Recording
  • experimenter with child, verbal/physical reminders, pause for reinforcers as needed
A Quantitative Electrophysiological Biomarker of Duplication 15q11.2-q13.1 Syndrome

Joel Frohlich1*, Damla Senturk2, Vidya Saravanpandian1, Peyman Golshani3, Lawrence T. Reiter1, Raman Sankar1, Ronald L. Thibert1, Charlotte DiStefano1, Scott Huberty1, Edwin H. Cook1, Shafail S. Jeste1

PROPERTY | RESULTS
---|---
Stable over time? | YES
 Scalable? | YES
 Relate to phenotype? | YES (epilepsy)
 Change with state? | YES (SLEEP!!)

Frohlich et al, Molecular Autism 2018; Saravanpandian et al, under revisions 2020

Mechanisms underlying the EEG biomarker in Dup15q syndrome


Frohlich et al, Mol Autism 2019
precision health...

- Genetic Etiology
- Effects on neural function
- Biomarker
- Clinical symptoms
- Targeted Treatment
- Outcome

Hypotonia/global delay, autism, epilepsy

motor, adaptive skills sleep
Goals for clinical trial readiness...

• *Determine the most meaningful and measurable* clinical endpoints

• *Identify* mechanistic biomarkers that can inform drug target engagement (and perhaps patient selection)

• *Design protocols and develop methods that maximize* access and scalability
Tuberous Sclerosis Complex (TSC)

Loss of function mutation in *TSC1/TSC2* genes

ASD in >50% (Jeste et al, 2007, 2009)

Early diagnosis: often in utero (Datta 2008; Davis, 2017)

By 12 months, infants who develop ASD show:

- Delays in nonverbal cognition (Jeste et al, *Neurology* 2014)
JASPER: Joint Attention, Symbolic Play, Engagement, Regulation

Kasari et al, 2015; Chang et al, 2016; Shire et al, 2017, 2019

ClinicalTrials.gov Identifier: NCT03422367
“I wanted to let you know that we have decided to not do the trial. My husband won’t be able to receive the time off to be able to travel with me. We are extremely disappointed and hope that maybe another trial comes up at a later time for my little ones.”

“Thank you for the information! We would love to participate, but unfortunately due to the travel we won’t be able to. We are already traveling 1-2 times per month for his appointments. If virtual ever becomes an option we’d be interested.”
1. LEARN

2. PRACTICE & RECORD

3. REVIEW
Hyde et al, *Journal of Neurodevelopmental Disorders*, 2020
Bcureful And The Tuberous Sclerosis Alliance Announced Plans To Formally Combine Efforts, Specifically By Establishing The Bcureful Travel Fund At The TS Alliance.
• Design protocols and develop methods that maximize access and scalability

Listen to and partner with families

Continue to innovate to develop effective and feasible remote assessment and delivery strategies

“Perfect is the enemy of the good”
Remote Assessment in Dup15q Syndrome

<table>
<thead>
<tr>
<th>Construct</th>
<th>Activity</th>
<th>Measures</th>
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</thead>
<tbody>
<tr>
<td>Visual attention</td>
<td>3-min video on tablet</td>
<td>Behavioral looking, heart-defined attention</td>
</tr>
<tr>
<td>Temperament</td>
<td>Arm restraint during play</td>
<td>Behavioral response, physiological arousal</td>
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<tr>
<td>Language</td>
<td>Unstructured play</td>
<td>Behavioral coding, LENA analysis, dyadic patterns (LENA and heart rate), BOSCC coding</td>
</tr>
<tr>
<td>Social Motor Play</td>
<td>Parent-child interaction</td>
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Test-retest

Natural change

BOSCC

PANDAbox

BOSCC

PANDAbox

BOSCC
FRESIAS
Endpoint Enabling Study in AS

Roche

Expressive communication
Independence and self-care
Maladaptive behaviors

Sleep
Fine & gross motor skills
Seizures
Cognition

Study Visits and Activities
approximately 12 months

Start of Study Clinic Visit
Physical examination
Questionnaires
Blood sample
Tests

Study Procedures at Home Daily
Sleep monitoring
Diary completion

Questionnaires
3 Home Visits
Electroencephalogram (EEG)

End of Study Clinic Visit
Physical examination
Questionnaires
Blood sample
Tests
Ovid TAK-935-18-002: Open label, phase 1 pilot study of TAK-935 (OV935) in individuals with 15Q Duplication Syndrome or CDKL5 Deficiency Disorder (ARCADE)

Ovid TAK-935-18-001: Phase 2, prospective, open-label extension study to assess the long-term safety and tolerability of TAK-935 (OV935) as adjunctive therapy in patients with rare epilepsy (Endymion)

Ages 2-18
Roche BP41674: Open-label, phase 1 clinical trial of RO7248824 (ASO) in individuals with Angelman Syndrome (AS)

Ages 1-12
GeneTx GTX-102-001: Phase 1/2 open-label, dose-escalating clinical trial of GTX-102 (ASO) in individuals with Angelman syndrome (AS)

Ages 4-17
“Isn’t genetic testing just academic?”

“How will this testing help my child/family?”
“How will this testing help my child/family?”

Hope

Optimism

Clarity
Thanks to all of our families!!

UCLA CART
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