Clinical trial readiness for syndromic neurodevelopmental disorders

Tarjan Lecture Series
April 20, 2020

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Financial Disclosures

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Editor-in-Chief of AAN Continuum Child Neurology Edition

Speakers Bureau for Medical Education Network

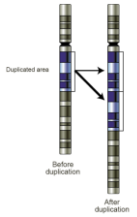
Talk outline

- Overview of syndromic neurodevelopmental disorders
- Clinical trial readiness – concepts and data
- Next steps

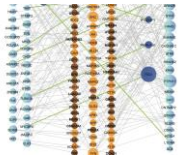
Advances in methods to examine ASD genetics

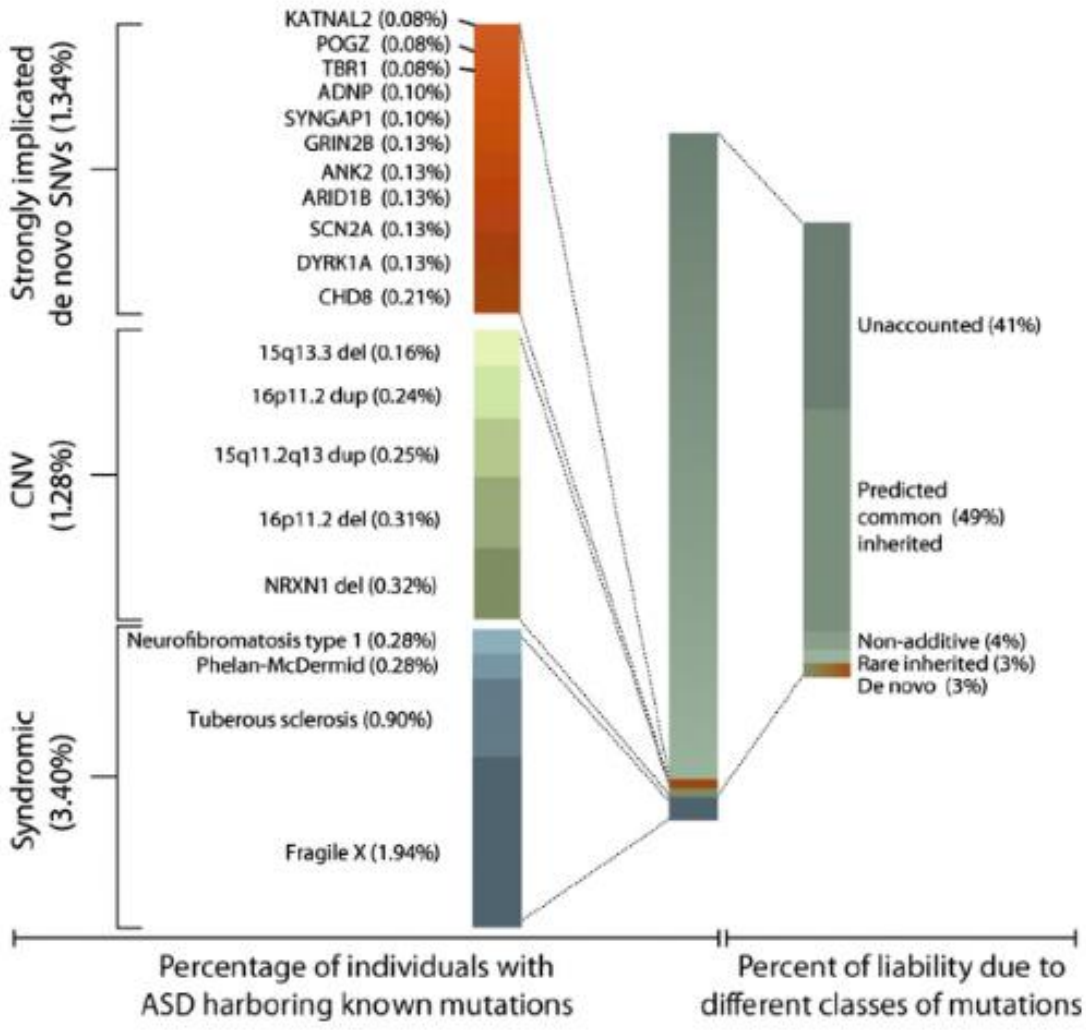
Karyotyping and FISH (Florescent in situ Hybridization)
3-5 million BPs

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

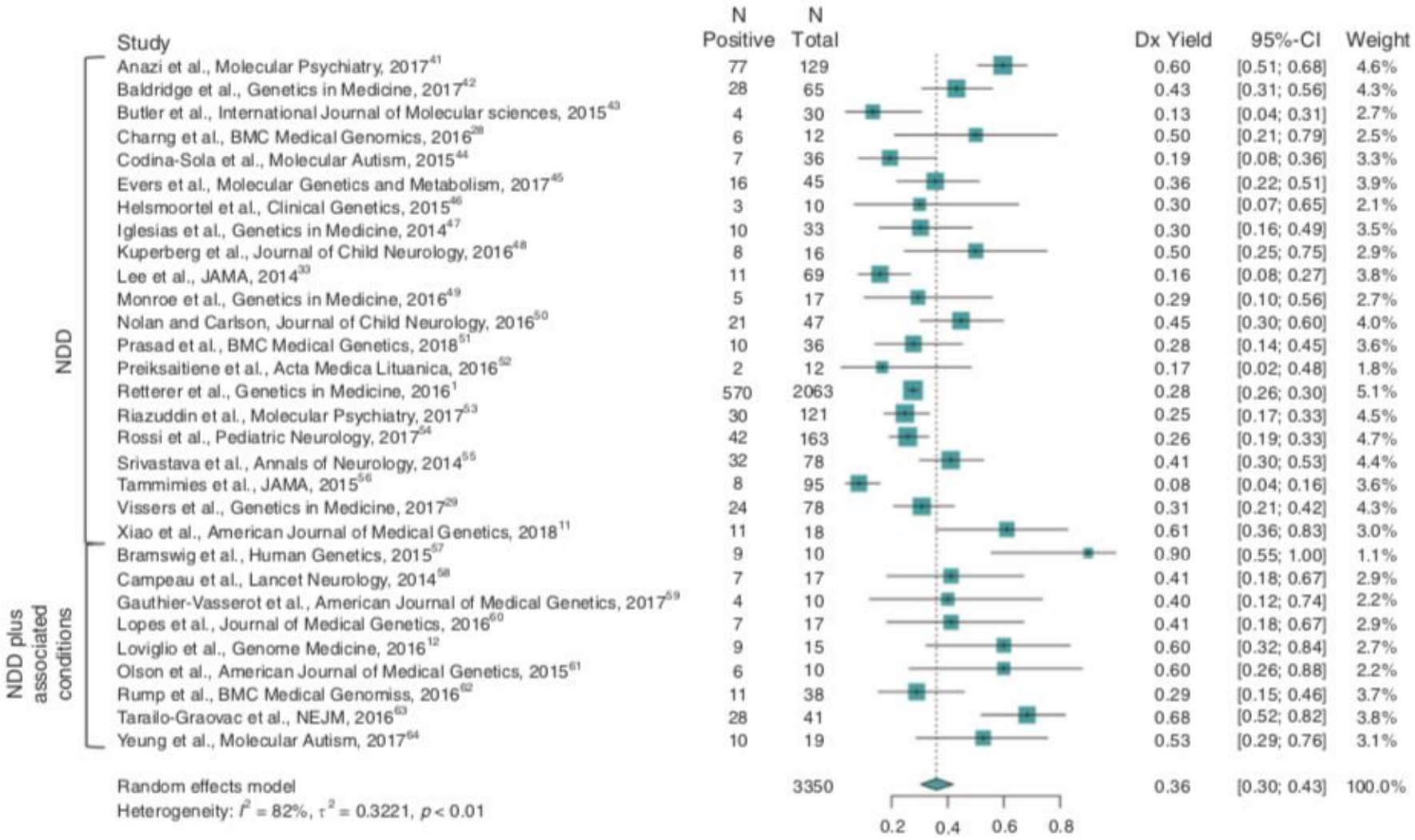
- Chromosomal microarray
- Boys: Fragile X
- Girls: MECP2 testing

(Whole exome sequencing if CMA is negative)

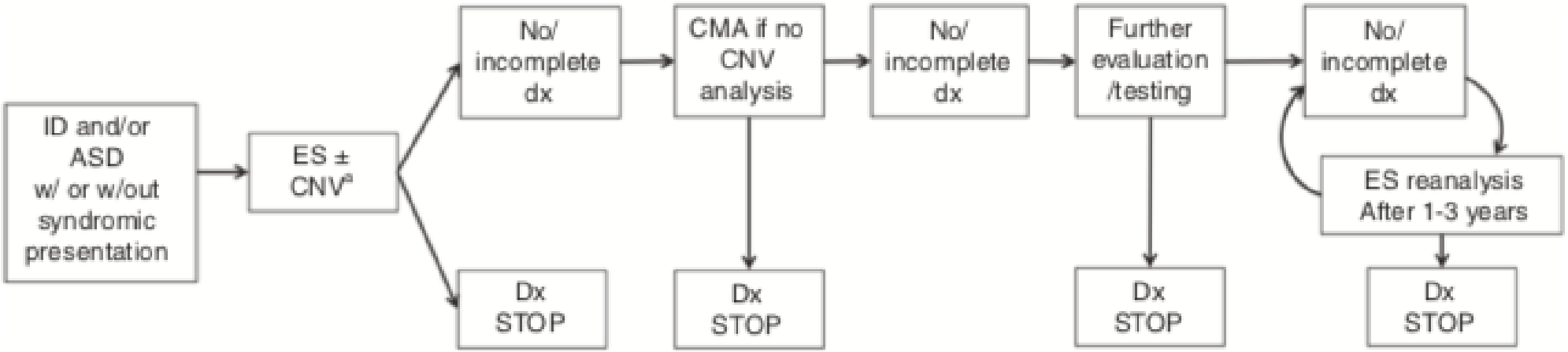
Schaefer et al, 2013

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], Kira A. Dies, ScM[1], David H. Ledbetter, PhD[2], Christa L. Martin, PhD[2], Wendy K. Chung, MD, PhD[3,4], Helen V. Firth, DM, FRCP[5,6], Thomas Frazier, PhD[7], Robin L. Hansen, MD[8], Lisa Prock, MD, MPH[1,9], Han Brunner, MD[10,11,12], Ny Hoang, MS[13,14,15], Stephen W. Scherer, PhD[14,15,16,17], Mustafa Sahin, MD PhD[1], David T. Miller, MD PhD[18] and the NDD Exome Scoping Review Work Group



Srivastava et al, 2019

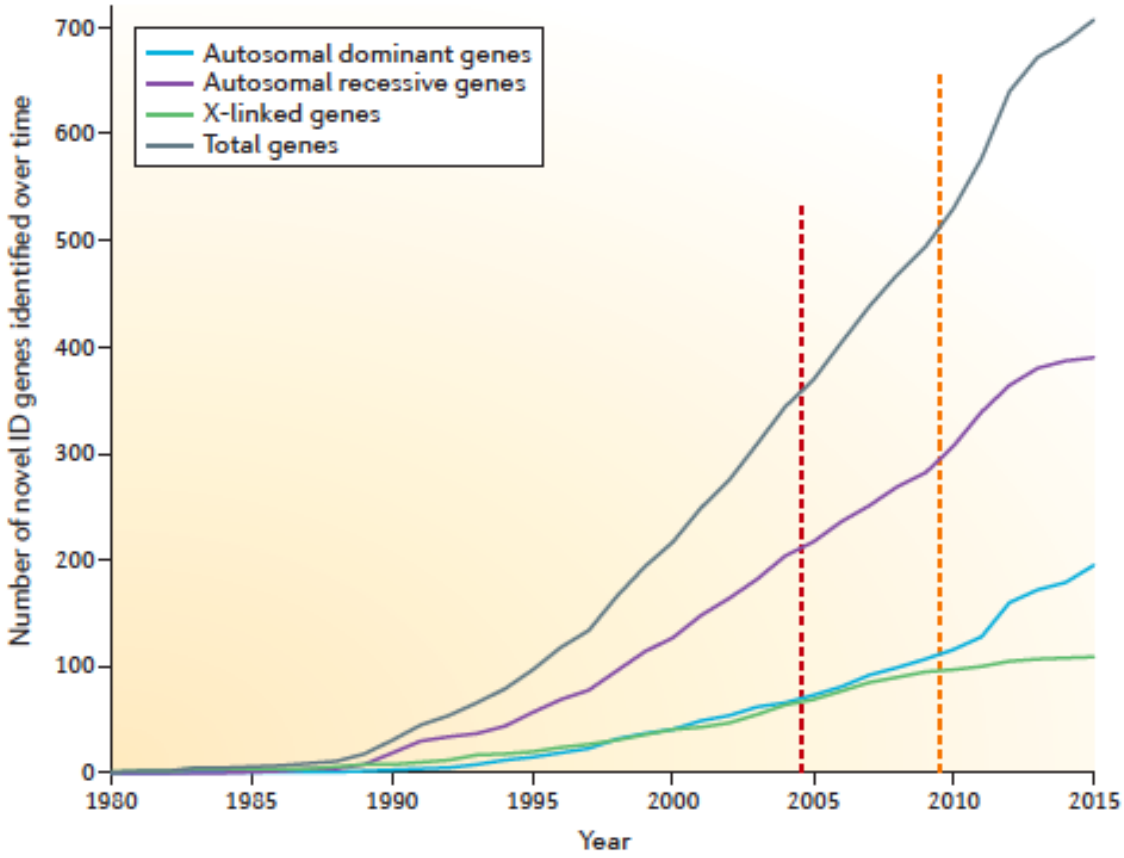


Continued issues:

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

Srivastava et al, 2019

>30% of ID/ASD have an identified genetic cause



Vessers, *Nature Rev Genetics*, 2016

"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

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- 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

DUP15q ALLIANCE

Tuberous Sclerosis Alliance

pmsf
Phelan-McDermid Syndrome Foundation

FRAXA Research Foundation

SCN2A RELATED AUTISM & EPILEPSY
FAMILIESCN2A FOUNDATION

AGENDA
Alliance for Genetic Etiologies in Neurodevelopmental Disorders and Autism

rett syndrome research trust

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
Neurology
Psychology
Social Work

Comprehensive After Visit Summary

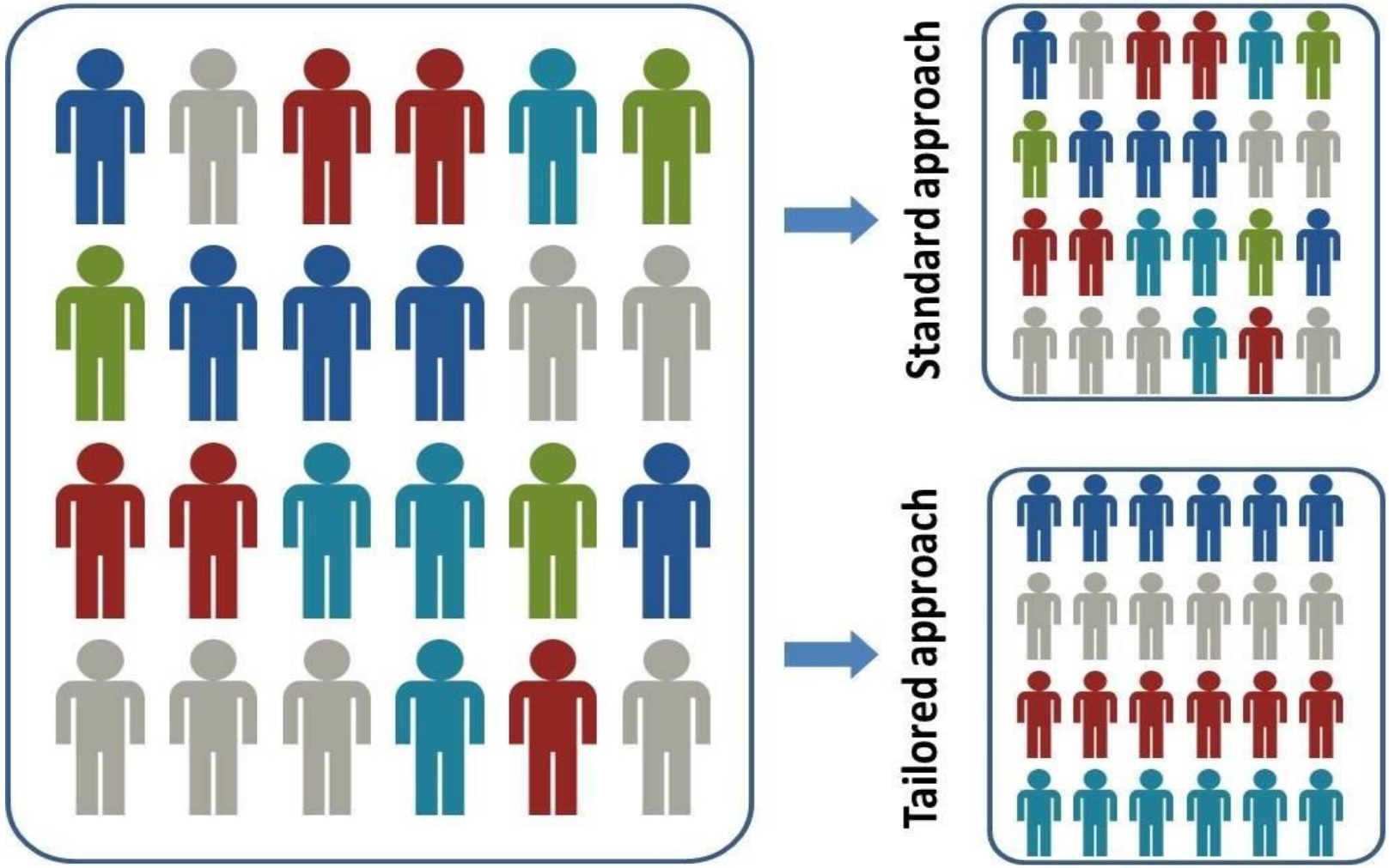
BBIGS
Brain & Behavior in Genetic Syndromes

Research

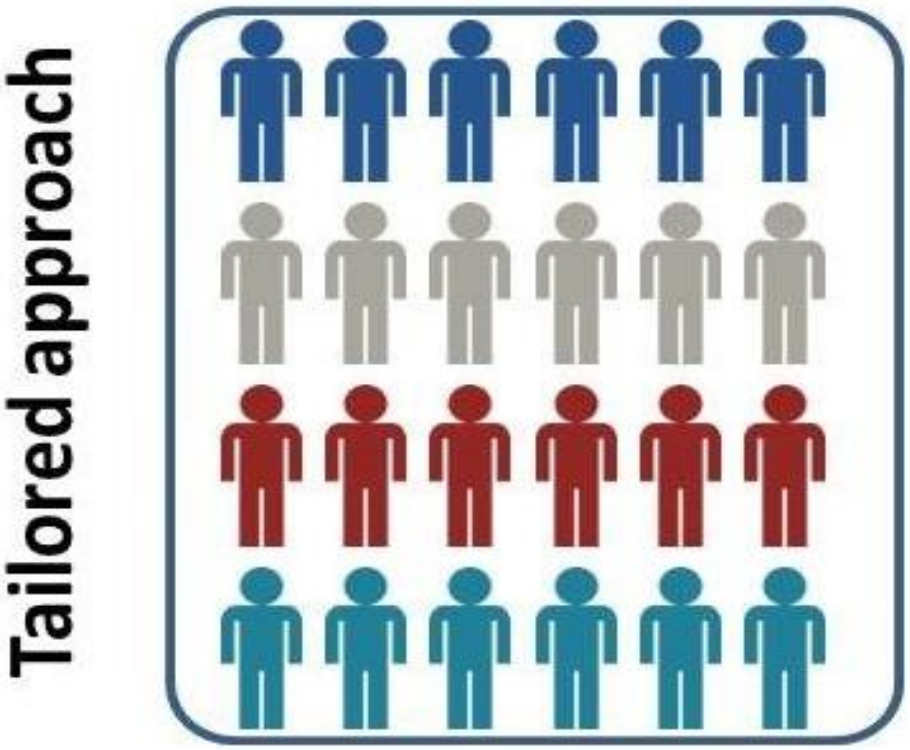
CARING database

- Community building
- Clinical monitoring and surveillance of comorbidities
- Potential for targeted therapeutics and clinical trials

A goal of precision health – syndrome specific treatments



A goal of precision health – syndrome specific treatments

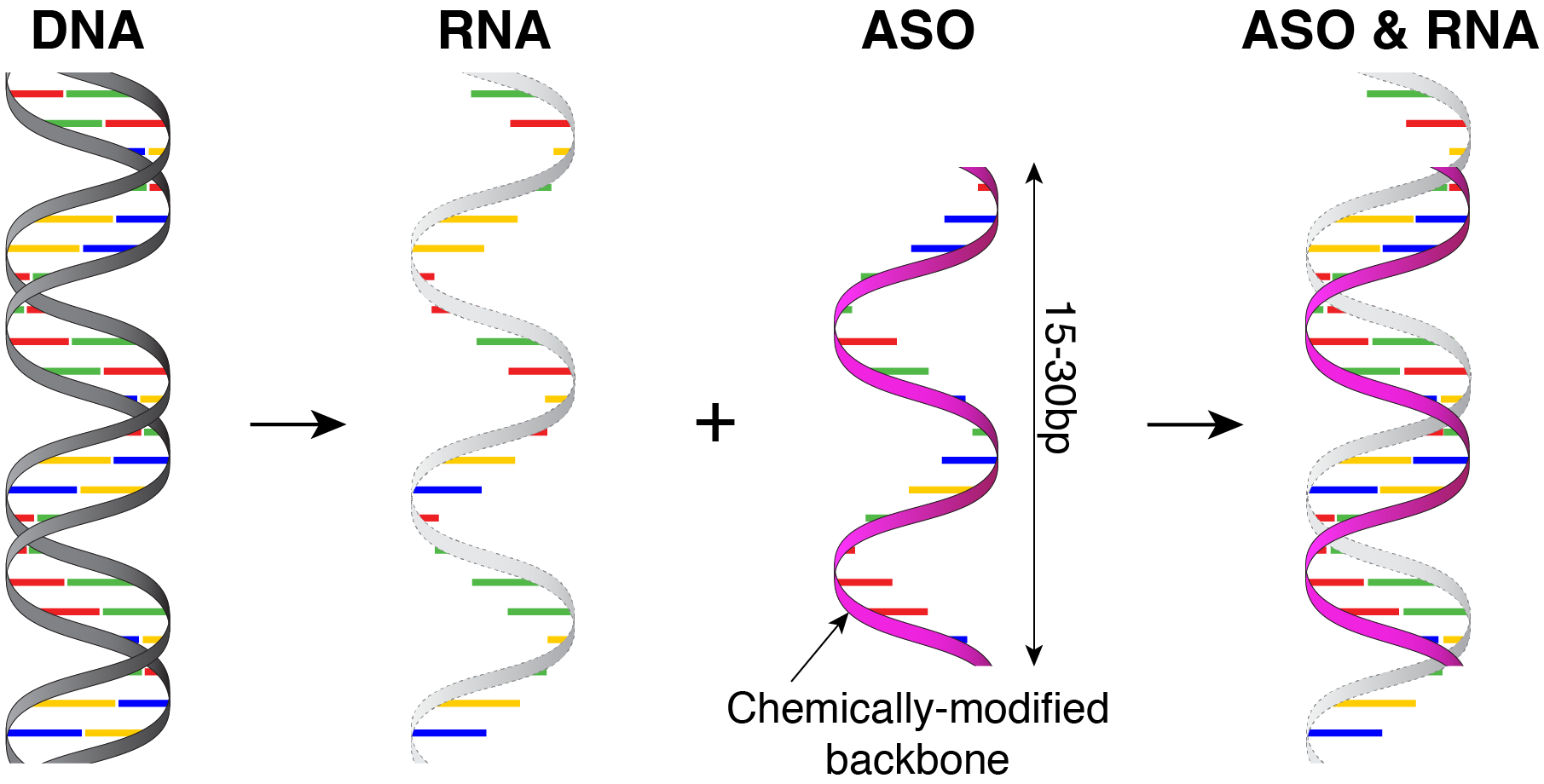


Medications

Gene Editing (CRISPR)

ASOs

Antisense oligonucleotides (ASOs) are short chemically-modified strands of nucleotides



courtesy of Stephan Sanders

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

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

20 May Roche, Biogen and Ionis Announce Collaborative Research Partnership

Webmaster Research No Comments

Roche Biogen IONIS

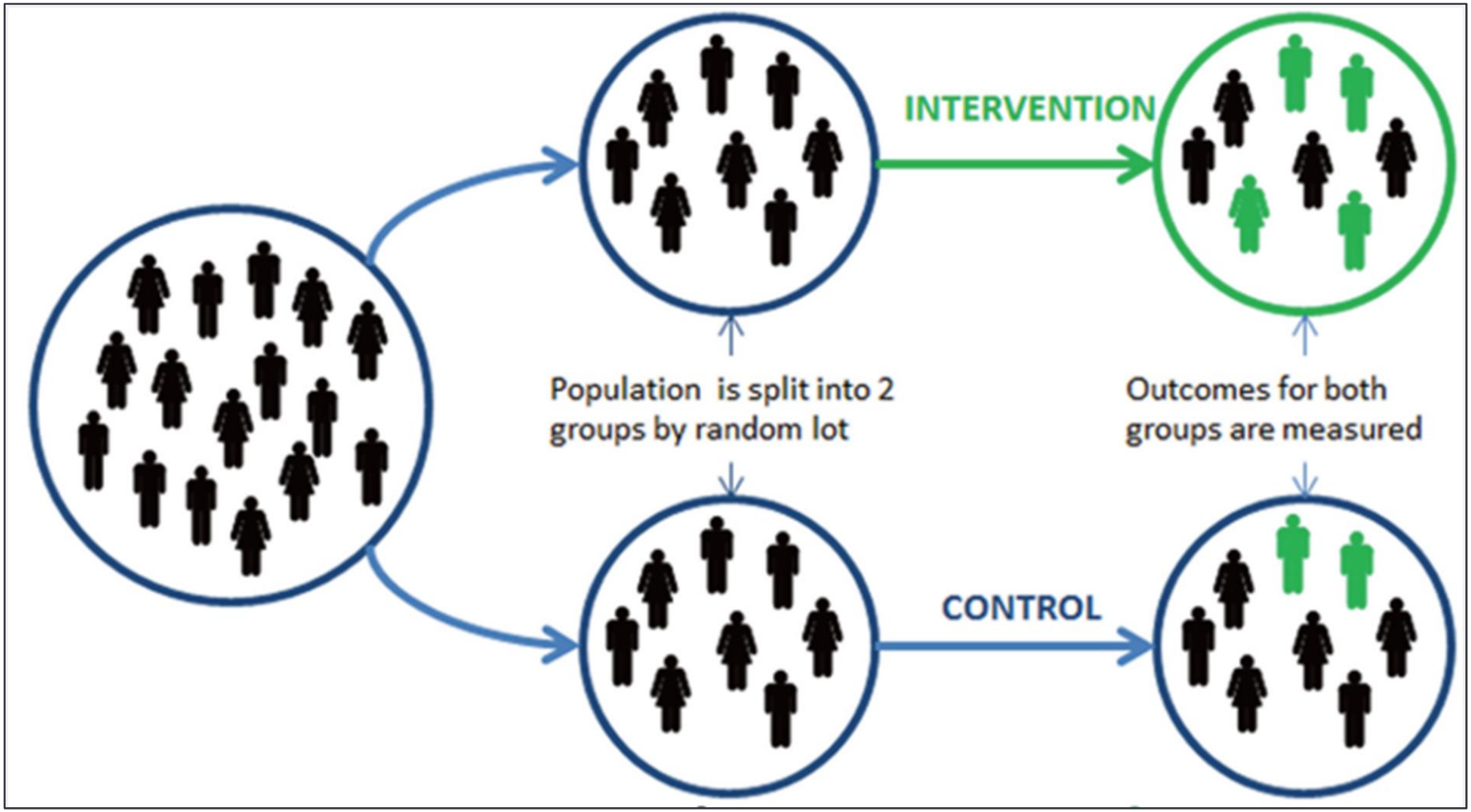
Aug 14, 2019 PDF Version

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

neuren pharmaceuticals



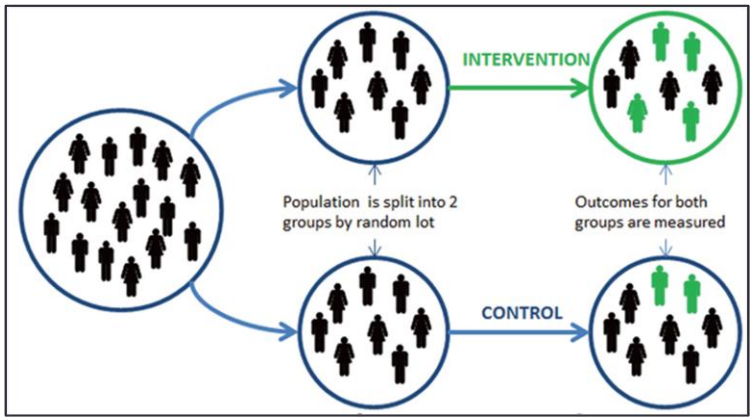
Haynes et al, 2012

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***

BBIGS
Brain & Behavior in Genetic Syndromes

JETS
JASPER Early Intervention for Tuberous Sclerosis

CARING CLINIC

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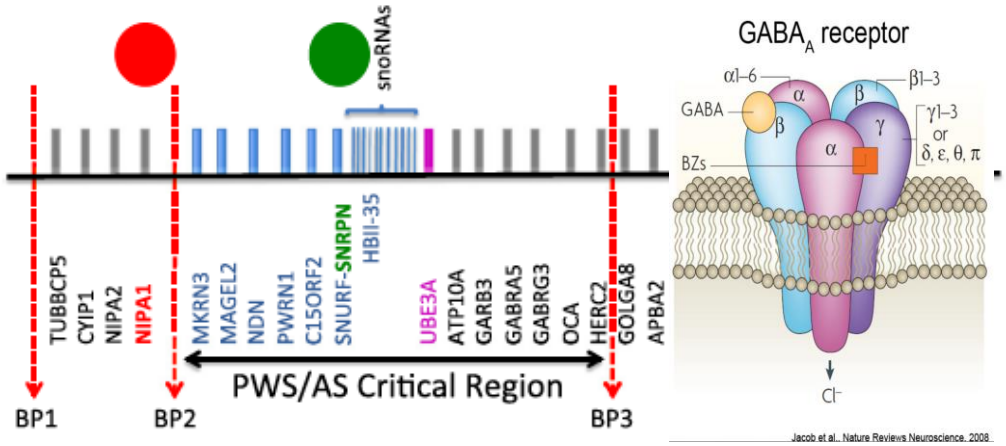
CARING CLINIC

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%)

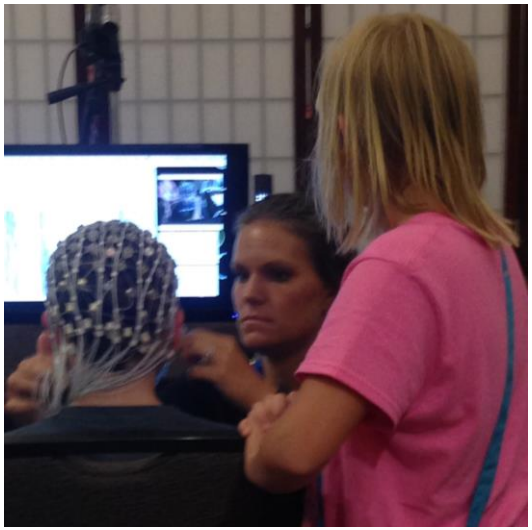
Al Ageeli, 2014; Urraca, 2013; Hogart, 2010; Battaglia, 2010; Conant, 2014; Finucane, 2016, Distefano, 2016; Urraca et al, 2018; Distefano et al, 2020

BBIGS
Brain & Behavior in Genetic Syndromes

Dup15q Alliance
FOR 15Q 11.2–13.1 MULTIPLICATIONS

Family meetings
Orlando 2015
Redondo Beach 2017
Houston 2019

62 children ages 2.5-18

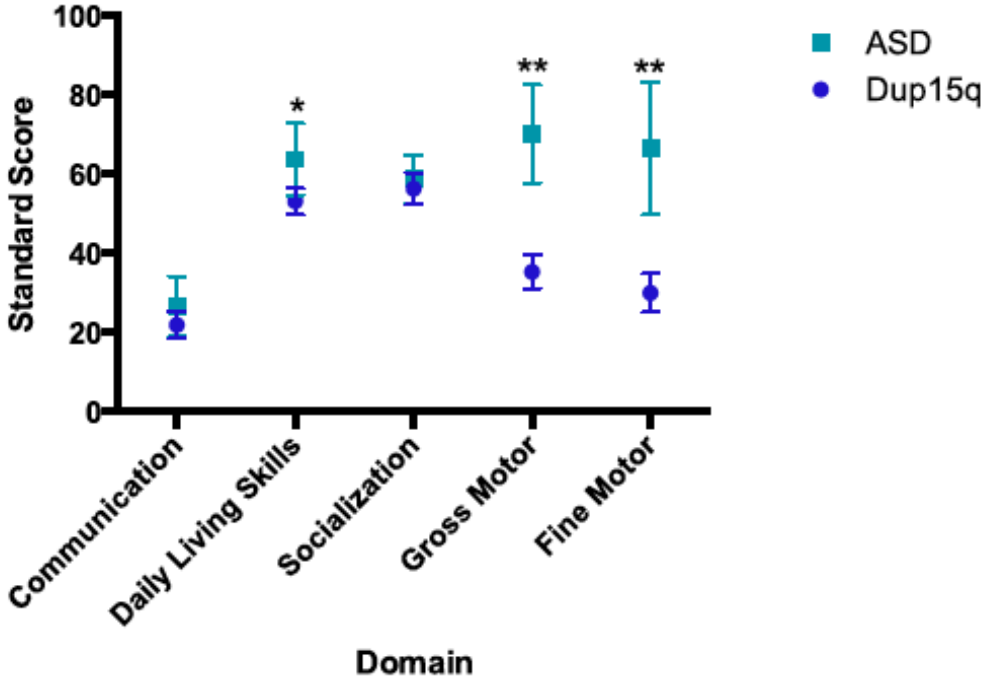


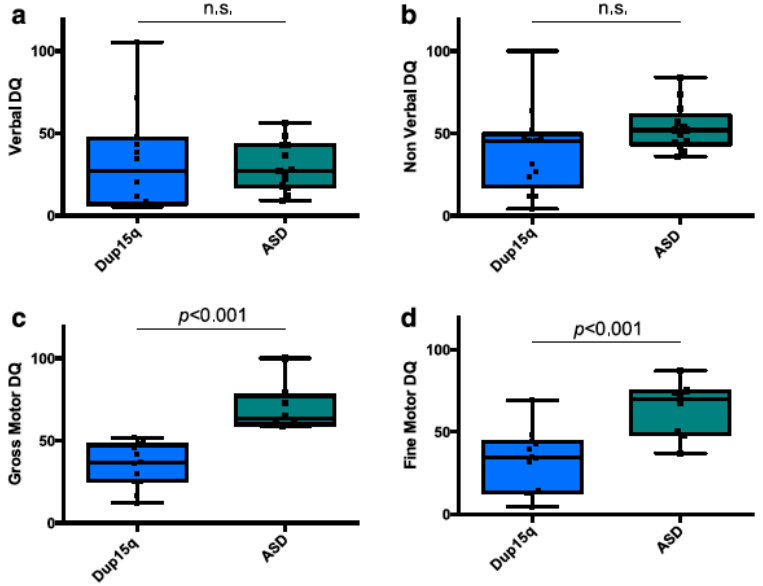
Developmental domains to assess

- Cognition
- Motor skills
- Adaptive skills
- Social skills

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

Charlotte DiStefano[1*], Amanda Gulsrud[1], Scott Huberty[1], Connie Kasari[2], Edwin Cook[3], Lawrence T. Reiter[4], Ronald Thibert[5] and Shafali Spurling Jeste[6]

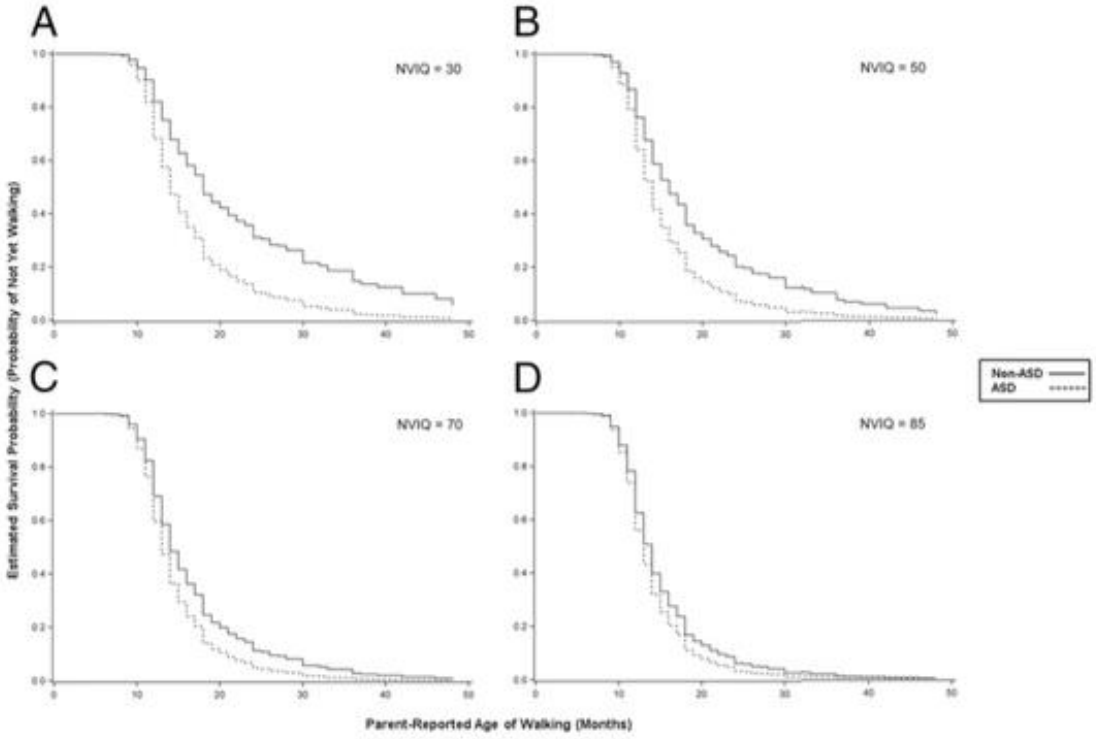


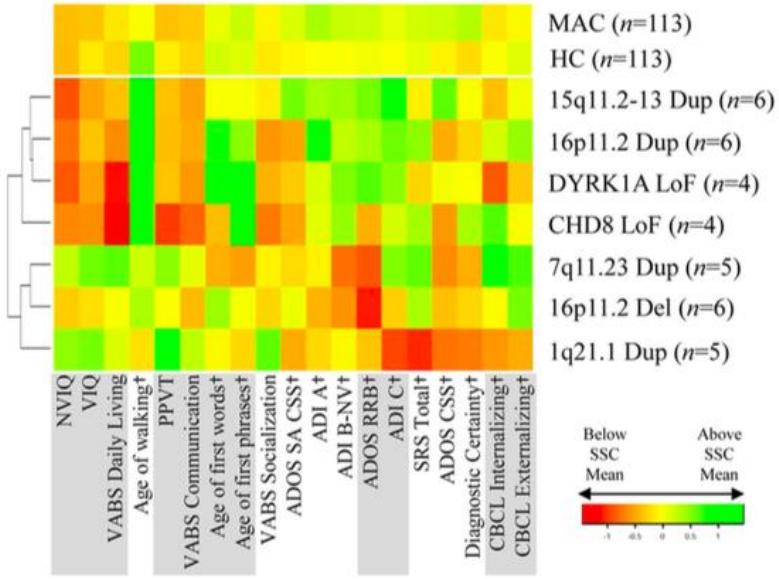


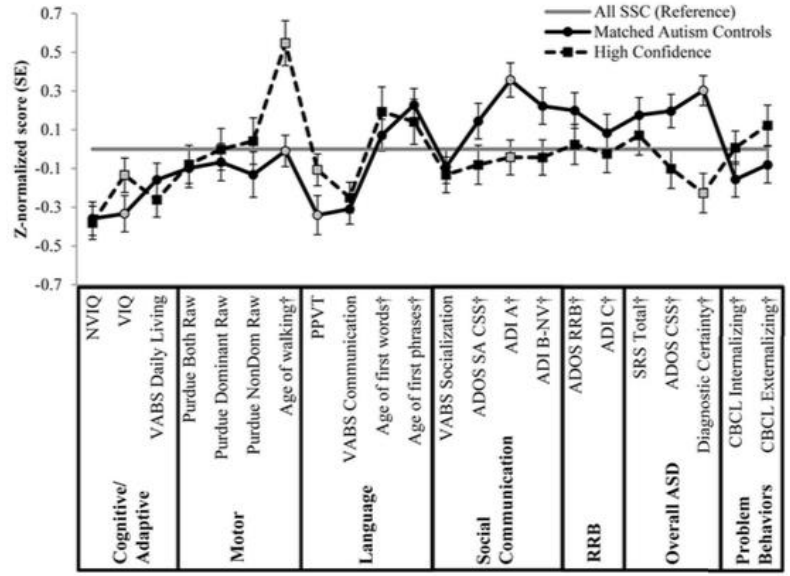
Distefano et al, *JNDD* 2016

Autism Spectrum Disorder, Intellectual Disability, and Delayed Walking

Somer L. Bishop, PhD,[a] Audrey Thurm, PhD,[b] Cristan Farmer, PhD,[b] Catherine Lord, PhD[c]







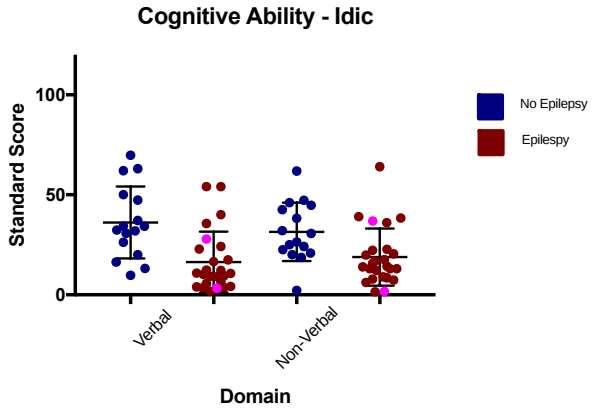
Bishop et al, 2016, 2017

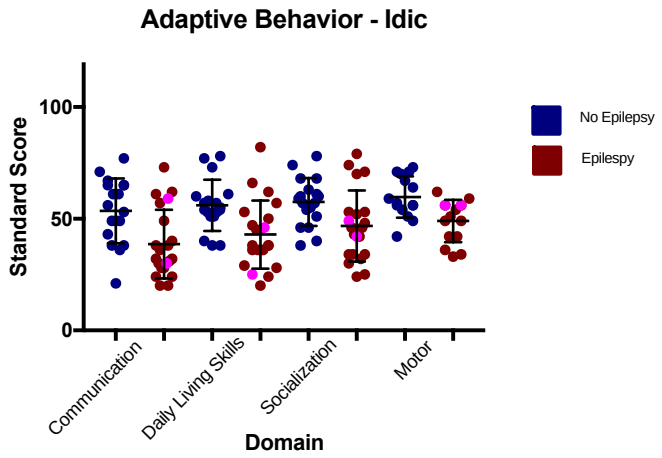
ORIGINAL ARTICLE

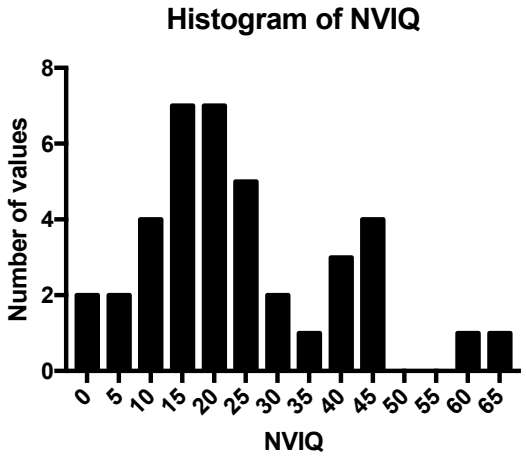
American Journal of medical genetics WILEY

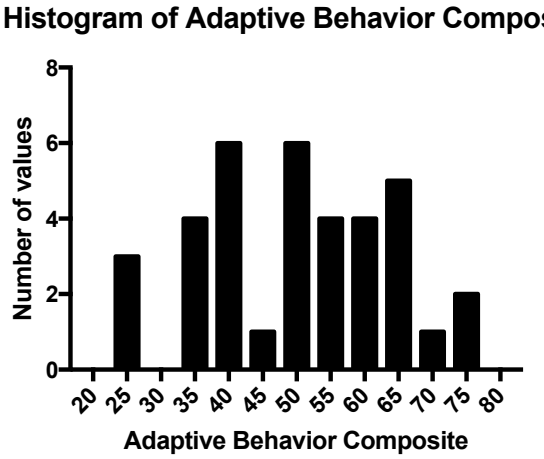
Behavioral characterization of dup15q syndrome: Toward meaningful endpoints for clinical trials

Charlotte DiStefano[1] | Rujuta B. Wilson[1] | Carly Hyde[1] | Edwin H. Cook[2] | Ronald L. Thibert[3] | Lawrence T. Reiter[4] | Vanessa Vogel-Farley[5] | Joerg Hipp[6] | Shafali Jeste[1]





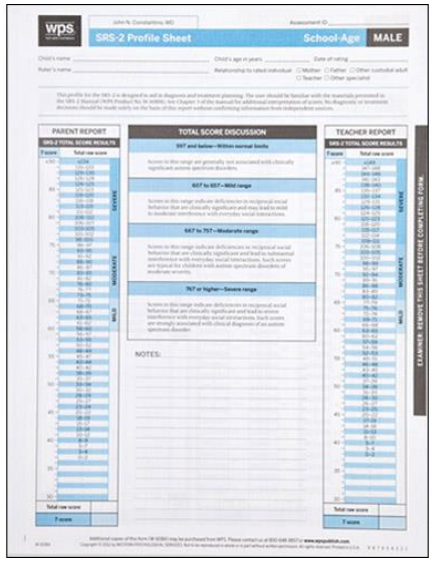




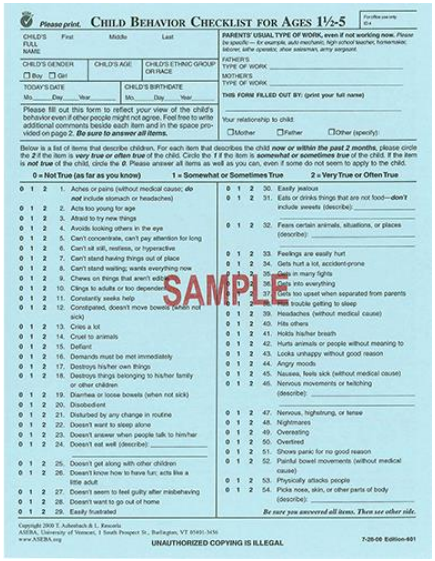
Distefano et al, *American Journal of Medical Genetics,* 2020

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"

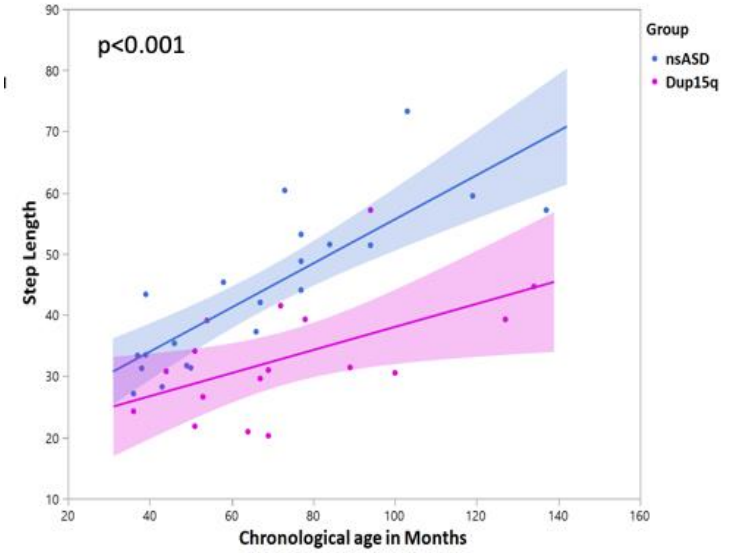


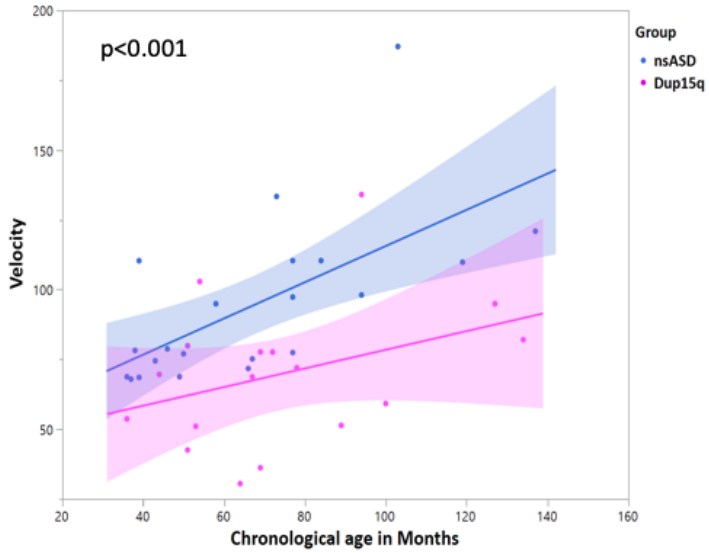
Distefano et al, *American Journal of Medical Genetics*, 2020

RESEARCH ARTICLE

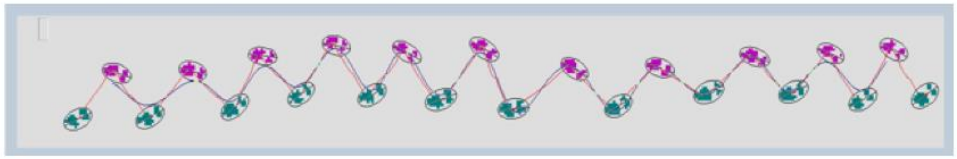
Quantitative Gait Analysis in Duplication 15q Syndrome and Nonsyndromic ASD

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

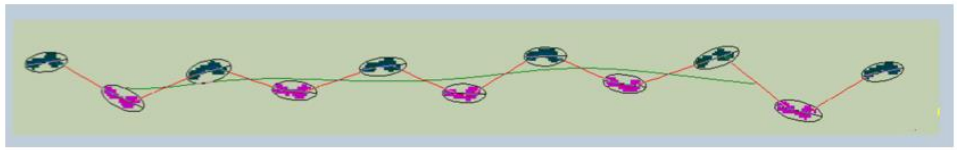




Dup15q



nsASD



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***

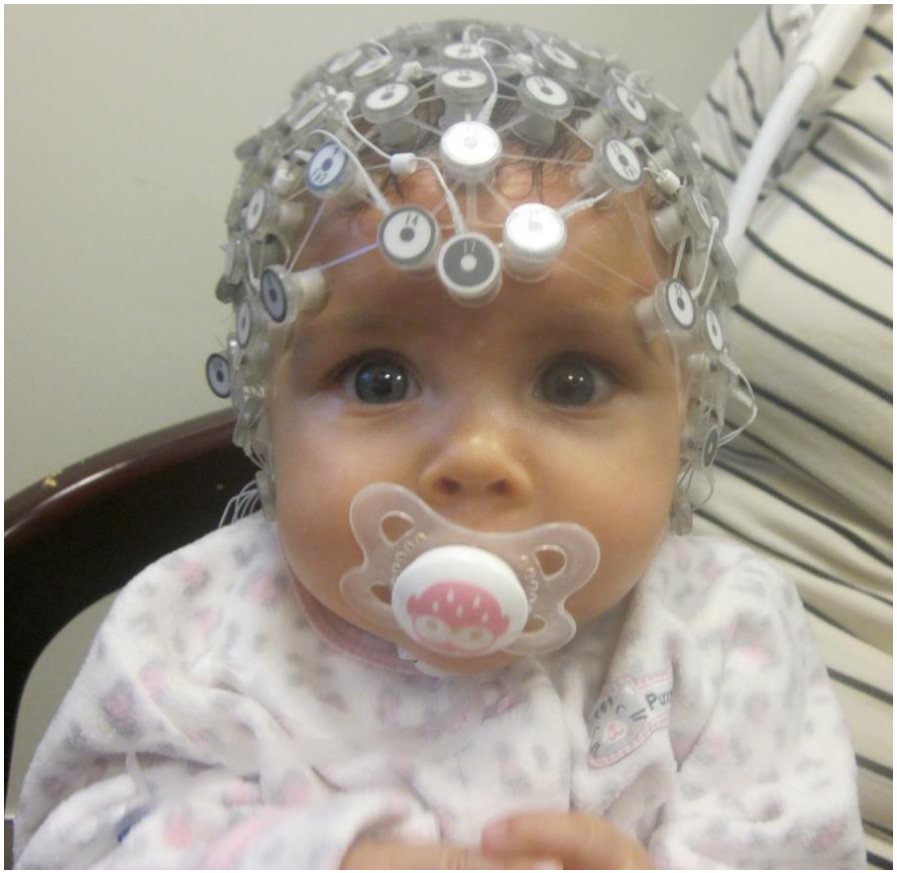
BBIGS
Brain & Behavior in Genetic Syndromes

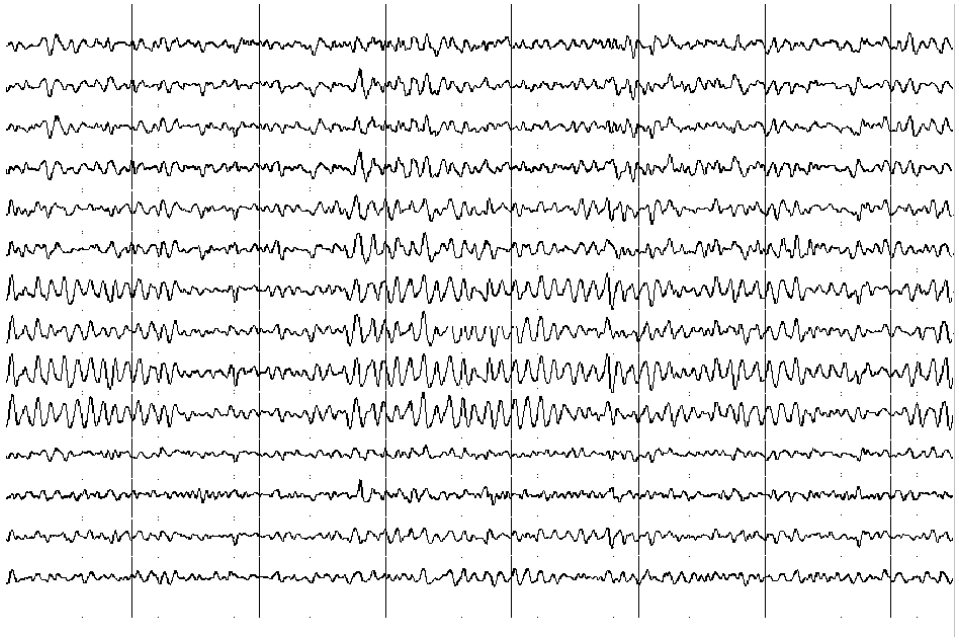
JETS
JASPER Early Intervention for Tuberous Sclerosis

CARING CLINIC

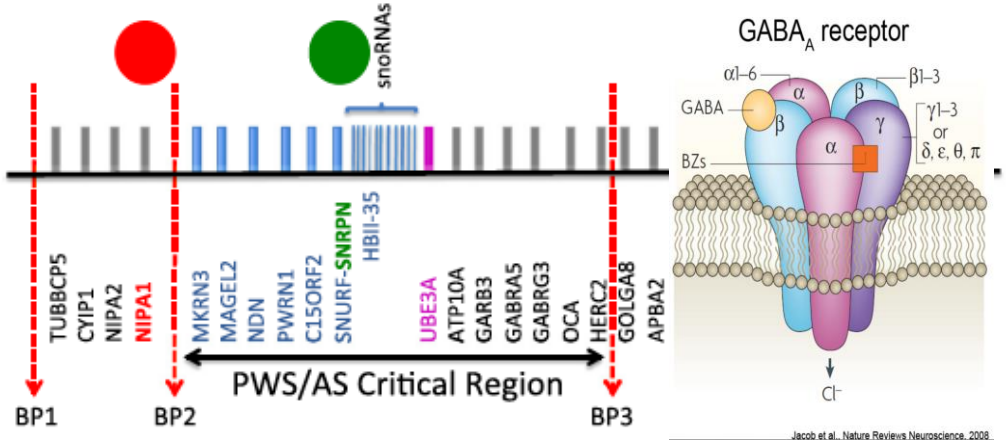
"Characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions"

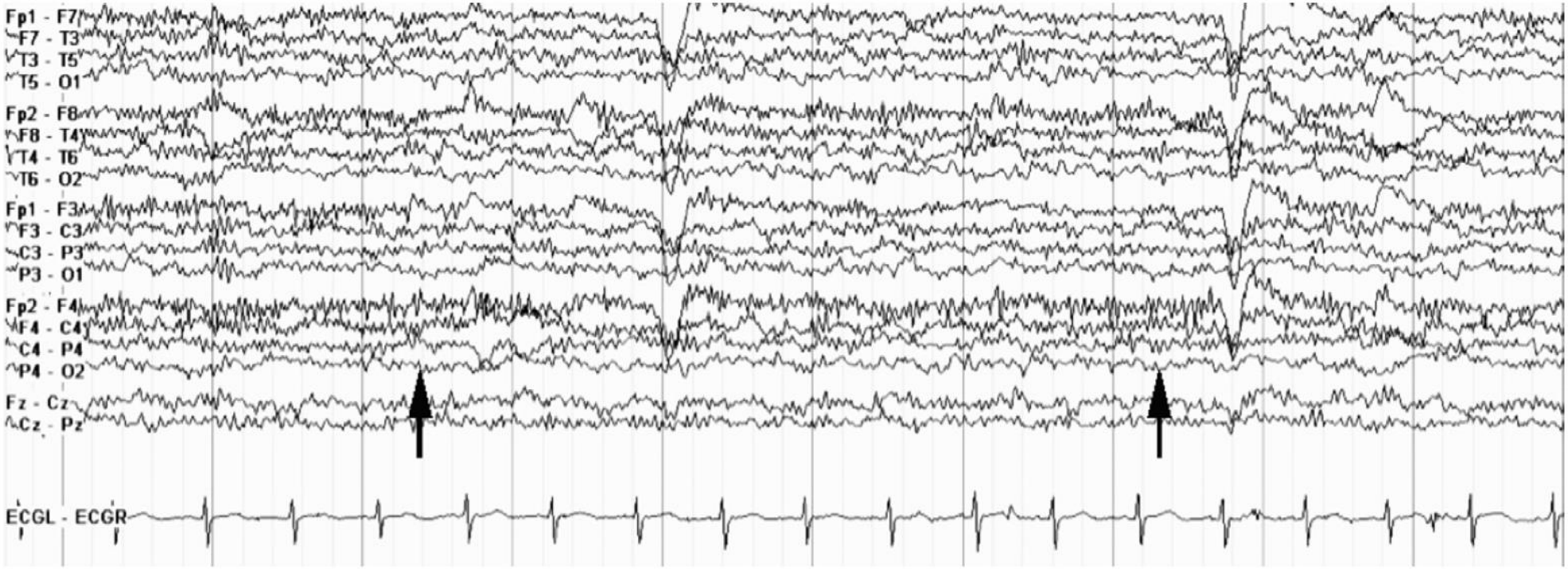
Robb and McInnes, *JAMA,* 2016; FDA-NIH Biomarker Working Group, 2016





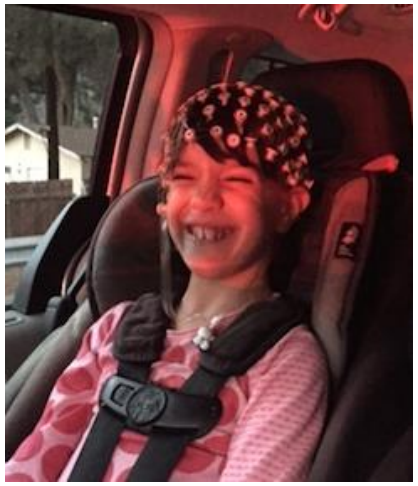
Dup15q syndrome

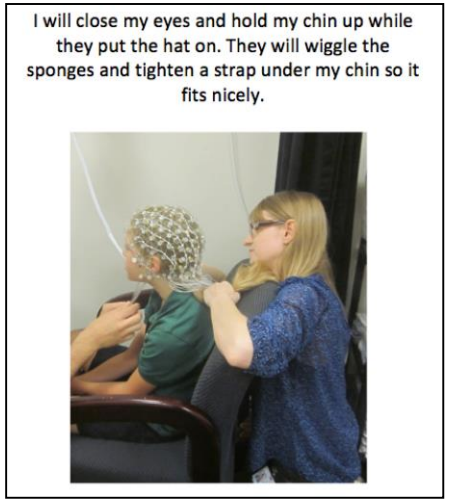




Urraca et al, 2018

- 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

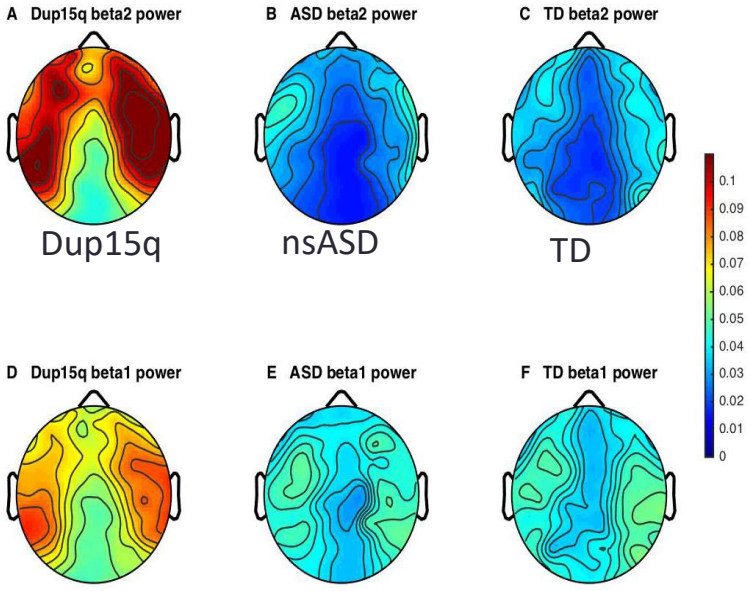


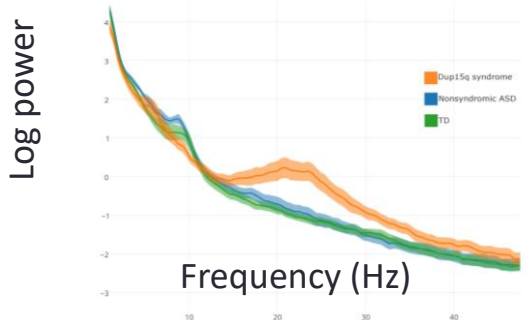


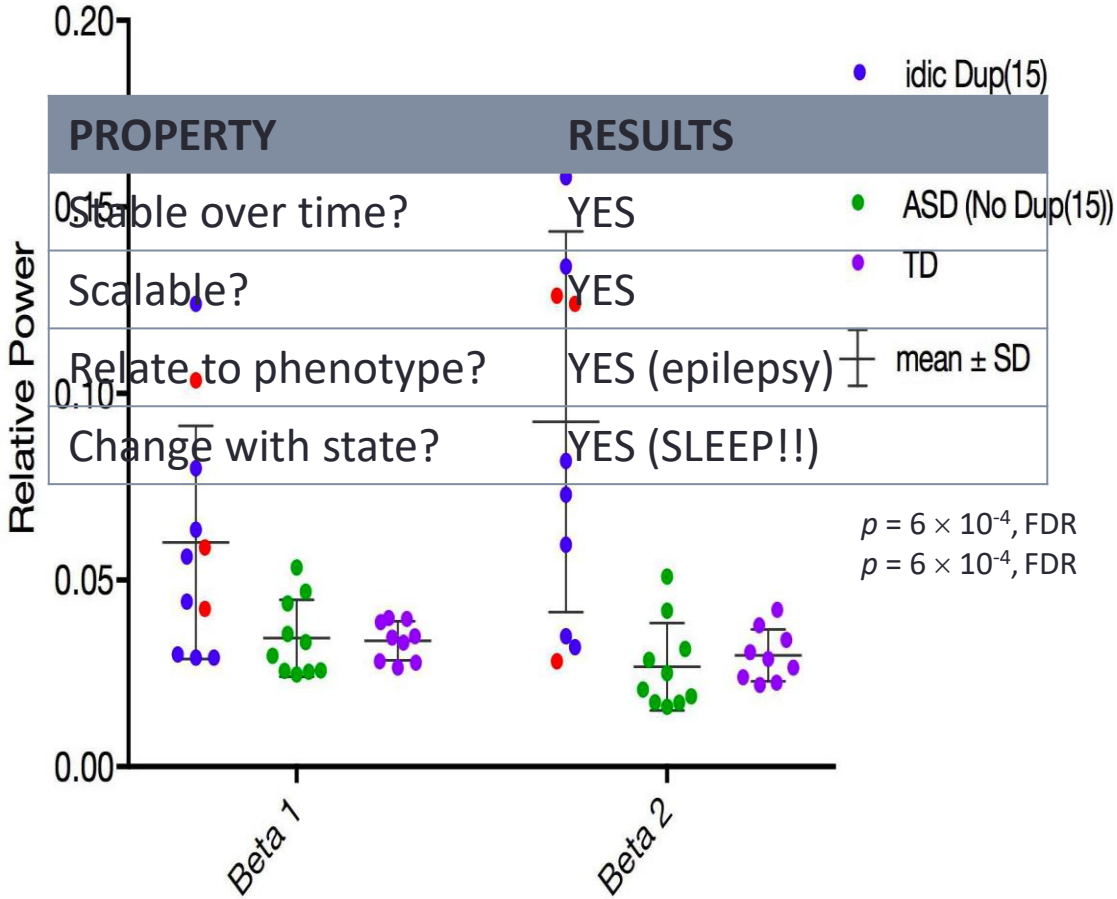
RESEARCH ARTICLE

A Quantitative Electrophysiological Biomarker of Duplication 15q11.2-q13.1 Syndrome

Joel Frohlich[1]*, Damla Senturk[2], Vidya Saravanapandian[1], Peyman Golshani[3], Lawrence T. Reiter[4], Raman Sankar[5], Ronald L. Thibert[6], Charlotte DiStefano[1], Scott Huberty[1], Edwin H. Cook[7], Shafali S. Jeste[1]







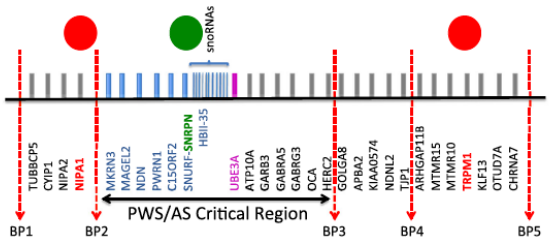
Frohlich et al, Molecular Autism 2018; Saravanpandian et al, under revisions 2020

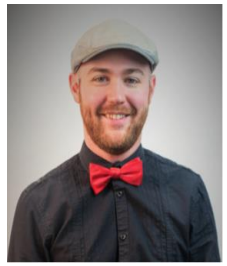
Frohlich et al, *PLoS One,* 2016

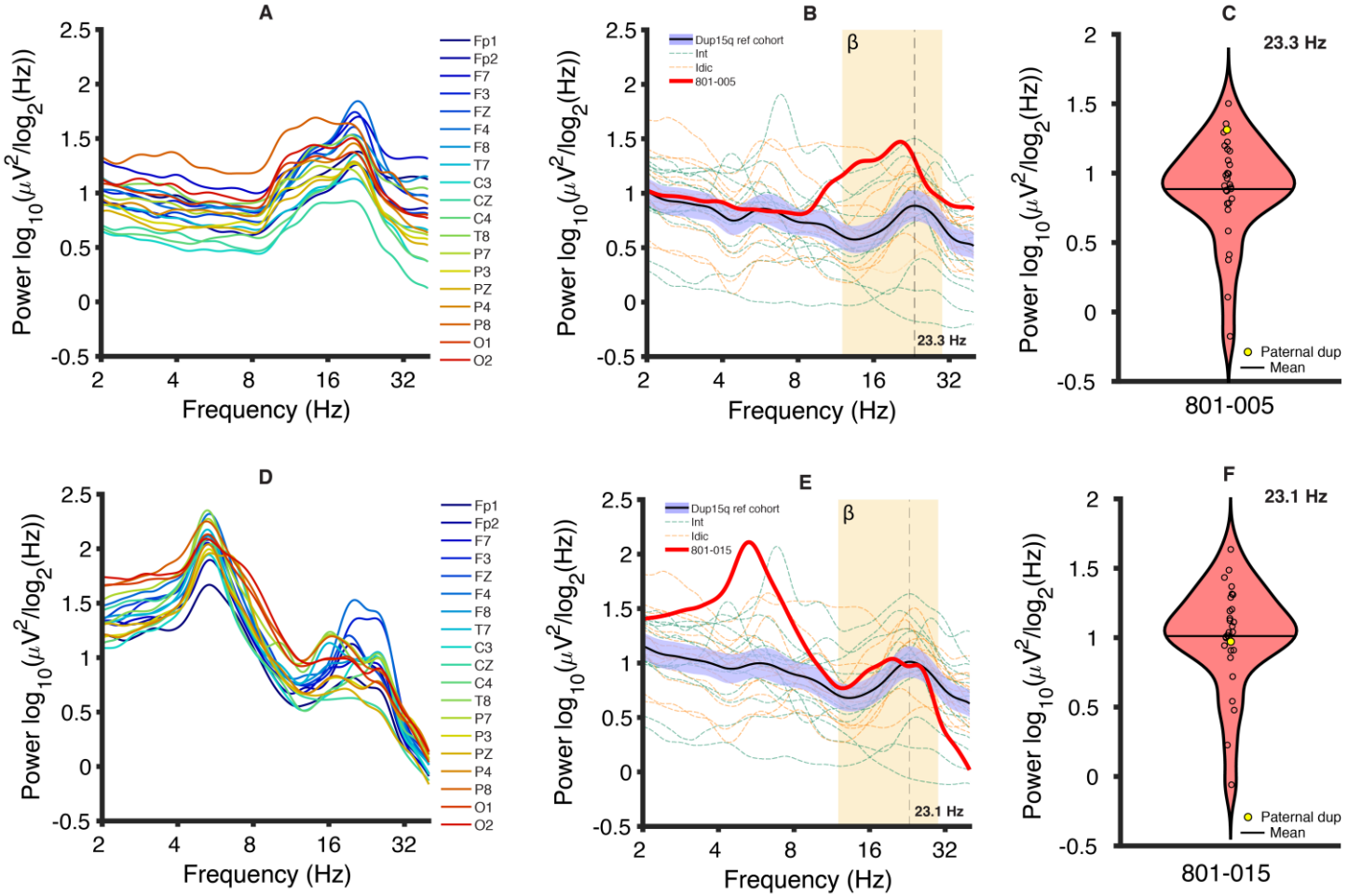
RESEARCH Open Access

Mechanisms underlying the EEG biomarker in Dup15q syndrome

Joel Frohlich[1,2,3*], Lawrence T. Reiter[4], Vidya Saravanapandian[2], Charlotte DiStefano[2], Scott Huberty[2,5], Carly Hyde[2], Stormy Chamberlain[6], Carrie E. Bearden[7], Peyman Golshani[8], Andrei Irimia[9], Richard W. Olsen[10], Joerg F. Hipp[1†] and Shafali S. Jeste[2†]

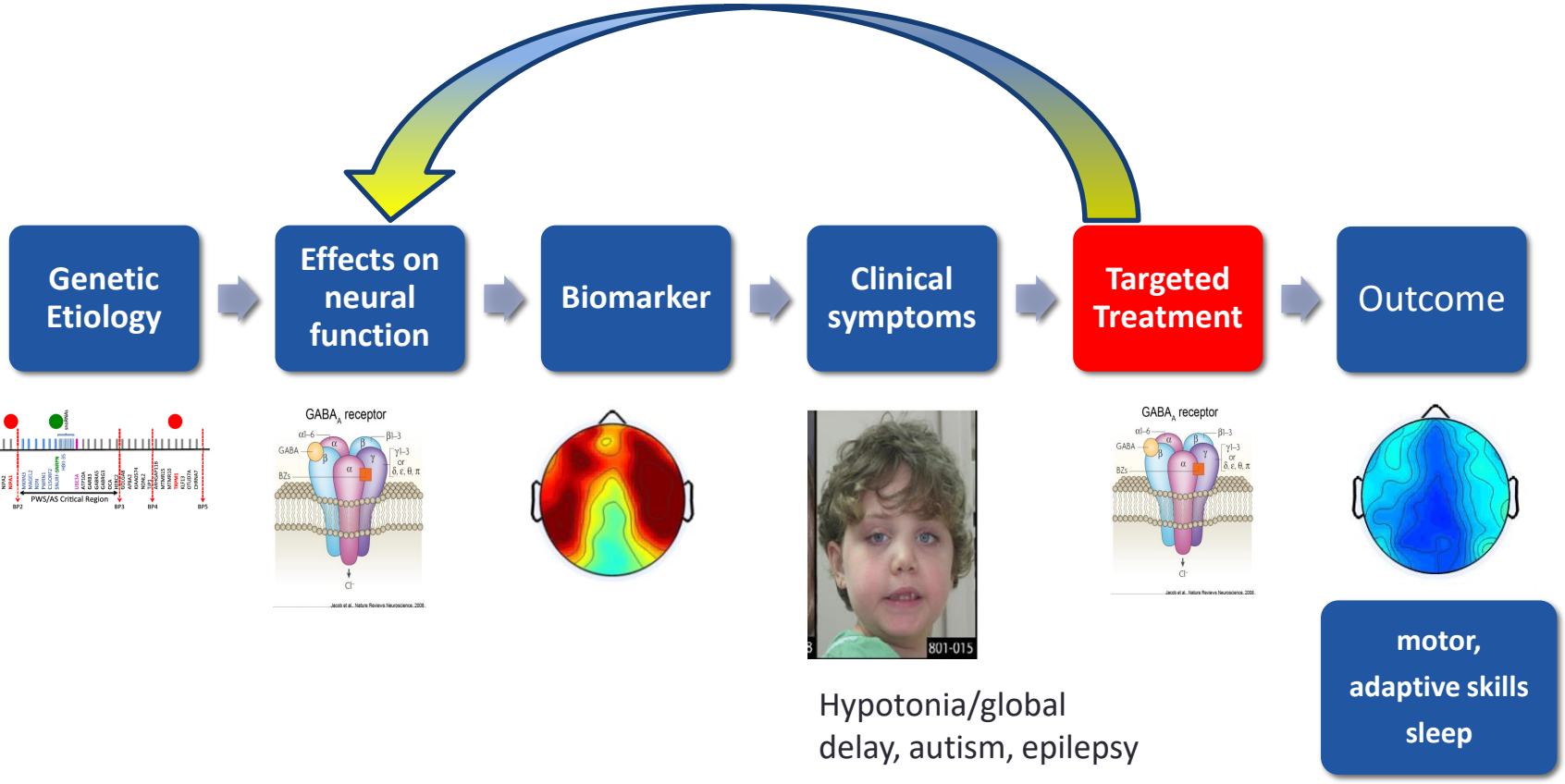






Frohlich et al, *Mol Autism* 2019

precision health…



Goals for clinical trial readiness...

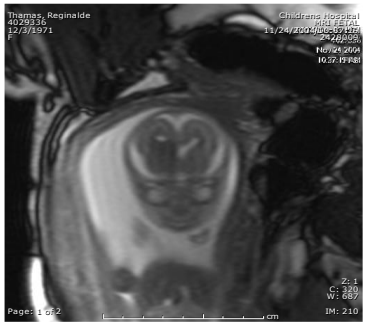
- *Determine the most meaningful and measurable **clinical endpoints***
- *Identify **mechanistic biomarkers** that can inform drug target engagement (and perhaps patient selection)*
- *Design protocols and develop methods that maximize **access and scalability***

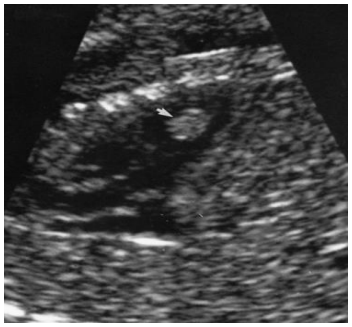
BBIGS
Brain & Behavior in Genetic Syndromes

JETS
JASPER Early Intervention for Tuberous Sclerosis

CARING CLINIC

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)
- Atypical social communication skills
  (McDonald et al, *Autism Research*, 2017)
- Atypical peak alpha band frequency and phase coherence
  (Dickinson et al, *Autism Research,* 2019)

JASPER
Early Intervention for Tuberous Sclerosis

JASPER: Joint Attention, Symbolic Play, Engagement, Regulation

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

ClinicalTrials.gov Identifier: NCT03422367

Hyde et al, *Journal of Neurodevelopmental Disorders,* 2020

"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."

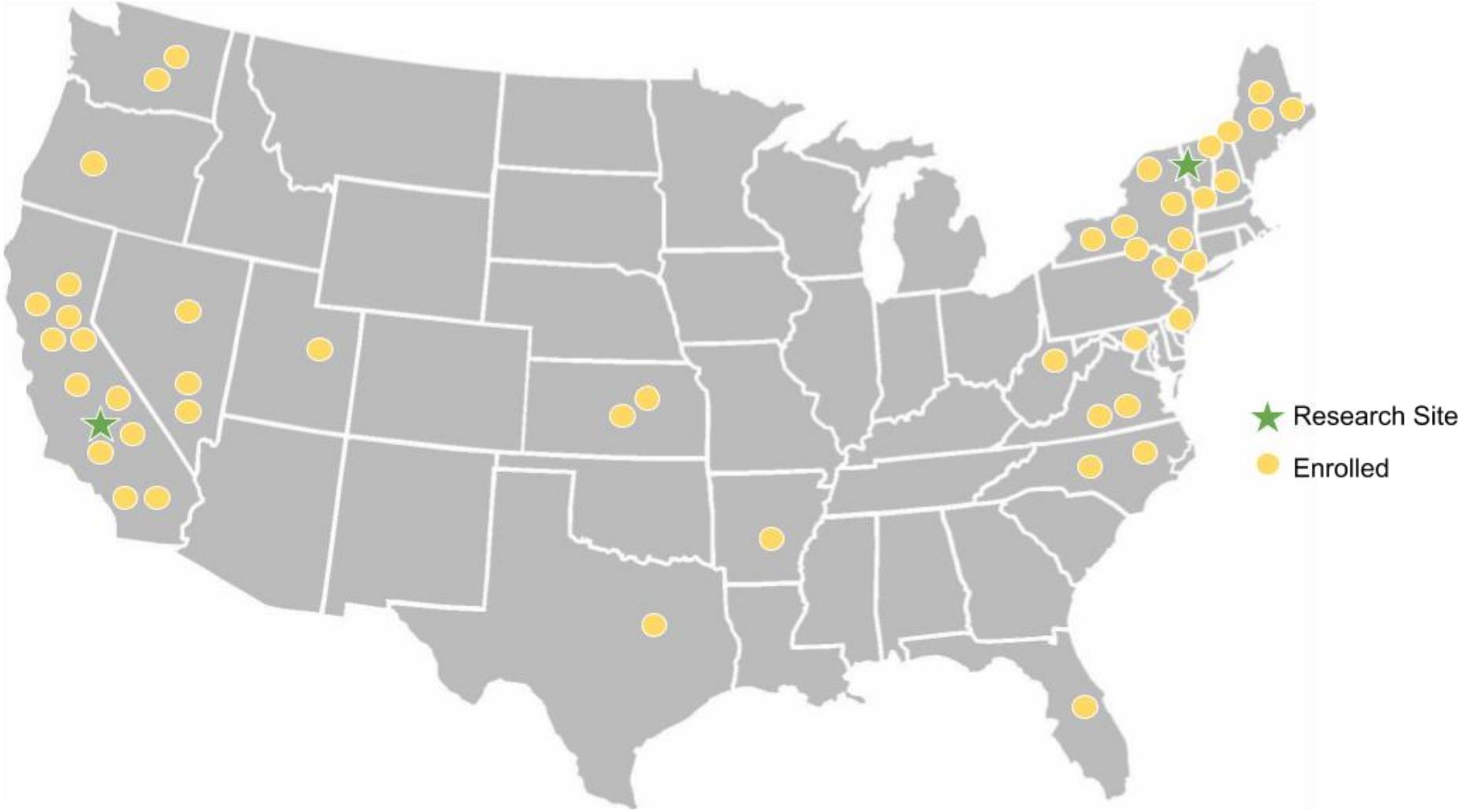
"Thank you for the information! We would love to participate, but unfortunately due to the travel we won't be able to. We are already traveling 1-2 times per month for his appointments. If virtual ever becomes an option we'd be interested."

1. LEARN

2. PRACTICE & RECORD

3. REVIEW

Hyde et al, *Journal of Neurodevelopmental Disorders,* 2020



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

Construct	Activity	Measures
Visual attention	3-min video on tablet	Behavioral looking, heart-defined attention
Temperament	Arm restraint during play	Behavioral response, physiological arousal
Language Social Motor Play	Unstructured play	Behavioral coding, LENA analysis, dyadic patterns (LENA and heart rate), BOSCC coding
	Parent-child interaction	

FREESIAS

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
- Tests
- Blood sample

Study Procedures at Home Daily

- Sleep monitoring
- Diary completion

Questionnaires

3 Home Visits

- Electroencephalogram (EEG)

End of Study Clinic Visit

- Physical examination
- Questionnaires
- Tests
- Blood sample

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

Ovid THERAPEUTICS

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

Ages 1-12

TANGELO

Targeting AS with an Oligonucleotide

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

https://uclahs.az1.qualtrics.com/jfe/form/SV_3dXLwMJYag0ukND

Thanks to all of our families!!

UCLA CART
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Stormy Chamberlain
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NIH
Congressionally Directed Medical Research Programs CDMRP Department of Defense
SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE
DUP15q ALLIANCE