

Appendix 1: Available Resources of the Developmental Synaptopathies Consortium

Since its inception in 2014, the Developmental Synaptopathies Consortium (DSC) has a detailed data collection and management system for the study of three rare neurogenetic disorders, Tuberous Sclerosis Complex, PTEN Hamartoma Tumor Syndrome and Phelan McDermid Syndrome.

A substantial amount of data has been collected from each cohort in the first phase of the DSC I (2014-2019) as described below. Additional data will be collected in the second phase of the DSC II (2020-2024). Cross-comparison of datasets is encouraged.

A) Tuberous Sclerosis Complex

DSC I Data:

N= 95 complete datasets (ages 3-21 years)

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Mullen Scales of Early Learning (MSEL)
- Wechsler Processing Speed Index (PSI)
- Peabody Picture Vocabulary Test - 4 (PPVT-4)
- Expressive Vocabulary Test - 2 (EVT-2)
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT/K-CPT)
- Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)
- Autism Diagnostic Interview - Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale - Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales (VABS-II): Caregiver Report
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Aberrant Behavior Checklist (ABC)
- Autism Clinical Certainty Rating
- Behavior and Sensory Interests Questionnaire (BSIQ)

Longitudinal Medical History collected over 3-5 years

Biological samples:

DNA samples: 91 patients, 121 parents (stored at University of Texas at Houston with PI Hope Northrup, MD)

RNA samples: 82 patients, 102 parents (stored at Van Andel Research Institute as part of TS Alliance collection)

Longitudinal data set of advanced diffusion tensor MRI including serial imaging for patients with Tuberous Sclerosis (performed yearly for 3+ years for 95 patients) and 54 healthy controls. We implemented a strict quality assurance platform in order to standardize the acquisition and analysis of these images.

DSC II Data:

We propose to study a total of 195 children ages 18 months and older (at the time of enrollment) with TSC and suspected or diagnosed ASD, ID, or combined ASD/ID.

Behavioral and neurocognitive measures as below:

- Stanford Binet-5 or Mullen Scales of Early Learning
- Wechsler Processing Speed Index Subtests
- Peabody Picture Vocabulary Test - 4
- Expressive Vocabulary Test - 2
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT-3 or K-CPT-2)
- Autism Diagnostic Observation Schedule (ADOS)
- Autism Diagnostic Interview - Revised (ADI-R)

- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale - Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales: Caregiver report (VABS-II and VABS-III)
- Aberrant Behavior Checklist, Second Edition (ABC-2)
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Child/Individual & Family Quality of Life Measure (CFQL-2 or IFQL)
- Regression Interview
- DSM-5 Autism Diagnostic Criteria Checklist
- Autism Clinical Certainty Rating

Longitudinal Medical History to be collected over 3-5 years, collection of MR images done on a yearly basis clinically, collection of clinical EEGs

Yearly collection of TAND Questionnaire:

Parent/participant questionnaire designed to capture mental health-related symptomology and diagnoses specific to the TSC population.

Blood sample collection for RNA and DNA (stored at Van Andel Research Institute as part of TS Alliance collection), optional consent for additional tissues/blood samples.

Neurophysiology:

A subset of participants (ages 2-10) will undergo an EEG session (inclusive of set up and four paradigms: resting state EEG, visual evoked potentials, auditory evoked potentials, complex social event related potentials. Healthy control data will also be collected.

B) PTEN Hamartoma Tumor Syndrome

DSC I Data:

N= 32 PTEN positive without ASD ages 3-21 years

N= 44 PTEN positive with ASD diagnosis ages 3-21 years

N= 33 Macrocephaly with ASD, no PTEN ages 3-21 years

N= 33 Healthy Controls ages 3-21 years

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Mullen Scales of Early Learning (MSEL)
- Wechsler Processing Speed Index (PSI)
- Peabody Picture Vocabulary Test - 4 (PPVT-4)
- Expressive Vocabulary Test - 2 (EVT-2)
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT/K-CPT)
- Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)
- Autism Diagnostic Interview - Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale - Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales (VABS-II): Caregiver Report
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Aberrant Behavior Checklist (ABC)
- Autism Clinical Certainty Rating
- Behavior and Sensory Interests Questionnaire (BSIQ)

Longitudinal Medical History collected over 3-5 years

Biological Samples:

96 patients provided biomaterial including DNA, plasma, RNA, WBC, LCL, microbiome urine, oral and fecal (stored at Cleveland Clinic with PI Charis Eng, MD).

Advanced diffusion tensor MRI for 18 patients with PHTS

Ongoing Clinical Trial with potential data to be analyzed:

The PTEN Everolimus Trial ([clinicaltrials.gov NCT02991807](https://clinicaltrials.gov/NCT02991807)) is ongoing to evaluate the safety of everolimus (RAD001) compared to placebo in patients with *PTEN* mutations, in addition to evaluating the efficacy of everolimus on

neurocognition and behavior in ages 5-45 year olds who have a *PTEN* mutation compared to placebo as measured by standardized direct and indirect neurocognitive tools and behavioral measures. We have randomized 40 patients for a 6 month blinded phase (1 everolimus: 1 placebo) and 6 month open label phase with a data collection completion date of December 2020. Participating centers include Boston Children's Hospital, Cleveland Clinic and Stanford University.

DSC II Data:

Population will include patients 18 months and older at the time of consent who have documentation of a verified *PTEN* mutation from a medical or mental health professional.

Behavioral and neurocognitive measures as below:

- Stanford Binet-5 or Mullen Scales of Early Learning
- Wechsler Processing Speed Index Subtests
- Peabody Picture Vocabulary Test - 4
- Expressive Vocabulary Test - 2
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Wechsler Processing Speed Index Subtests (PSI)
- Connors Continuous Performance Test (CPT or K-CPT-2)
- Autism Diagnostic Observation Schedule (ADOS)
- Autism Diagnostic Interview - Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale - Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales: Caregiver report (VABS-II and VABS-III)
- Aberrant Behavior Checklist, Second Edition (ABC-2)
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Child/Individual & Family Quality of Life Measure (CFQL-2 or IFQL)
- Regression Interview
- DSM-5 Autism Diagnostic Criteria Checklist
- Autism Clinical Certainty Rating

Longitudinal Medical History over 3-5 years

Yearly Blood Sample Collection, optional consent for additional tissues/blood samples/microbiome(stored at Cleveland Clinic with PI Charis Eng, MD).

Yearly collection of TAND Questionnaire:

Parent/participant questionnaire designed to capture mental health-related symptomology and diagnoses specific to the TSC population.

Neurophysiology:

A subset of participants (ages 2-10) will undergo an EEG session (inclusive of set up and four paradigms: resting state EEG, visual evoked potentials, auditory evoked potentials, complex social event related potentials. Healthy control data will also be collected.

C) Phelan McDermid Syndrome

DSC I Data:

N= 97 full datasets for children ages 3-21 years

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Mullen Scales of Early Learning (MSEL)
- Wechsler Processing Speed Index (PSI)
- Peabody Picture Vocabulary Test - 4 (PPVT-4)
- Expressive Vocabulary Test - 2 (EVT-2)
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Connors Continuous Performance Test (CPT/K-CPT)
- Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)
- Autism Diagnostic Interview - Revised (ADI-R)
- Social Responsiveness Scale - 2 (SRS-2)
- Repetitive Behavior Scale - Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales (VABS-II): Caregiver Report
- Developmental Coordination Disorder Questionnaire (DCDQ)
- Aberrant Behavior Checklist (ABC)
- Autism Clinical Certainty Rating
- Behavior and Sensory Interests Questionnaire (BSIQ)

Longitudinal Medical History collected over 3-5 years

Biological Samples:

N= 98 total patients

N= 189 parents and/or sibling

Of these, 58 are trios (stored at Mt Sinai with PI Alexander Kolevzon, MD).

Advanced diffusion tensor MRI for 18 patients with Phelan McDermid Syndrome

DSC II Data:

We propose to collect 190 subjects 18 months of age and older with pathogenic deletions or mutations of the *SHANK3* gene will undergo medical, genetic, behavioral, cognitive, language, sensory, and motor testing.

Behavioral and neurocognitive measures as below:

- Stanford Binet-5/Differential Ability Scales (DAS-II)/Mullen Scales of Early Learning
- Psychoeducational Profile, Third Edition (PEP-III)2
- Peabody Picture Vocabulary Test - 4
- Expressive Vocabulary Test - 2
- Beery Visual-Motor Integration, 6th Edition (VMI)
- Autism Diagnostic Observation Schedule (ADOS)
- Sensory Assessment for Neurodevelopmental Disorders (SAND)
- Autism Diagnostic Interview - Revised (ADI-R)
- Repetitive Behavior Scale - Revised (RBS-R)
- Child Behavior Checklist/Adult Observer Report Form (CBCL/ARF)
- Child/Individual & Family Quality of Life Measure (CFQL or IFQL)
- Short Sensory Profile Questionnaire (SSP)
- Vineland Adaptive Behavior Scales: Comprehensive Interview Form (VABS-II and VABS-III)
- Aberrant Behavior Checklist, Second Edition (ABC)
- Developmental Coordination Disorder Questionnaire (DCDQ)
- MacArthur Bates Communication Development Inventory (MCDI)
- Pervasive Developmental Disorder Behavior Inventory (PDD-BI)
- Children's Sleep Habits Questionnaire
- Early Detection Screen for Dementia
- Waisman Activities of Daily Living Form
- Regression Interview
- DSM-5 Autism Diagnostic Criteria Checklist
- Autism Clinical Certainty Rating

Longitudinal Medical History over 3-5 years

Biological samples will be collected for whole exome sequencing and RNA extraction (stored at Mt Sinai with PI Alexander Kolevzon, MD), optional consent for additional samples.

Yearly collection of TAND Questionnaire:

Parent/participant questionnaire designed to capture mental health-related symptomology and diagnoses specific to the TSC population.

Neurophysiology:

A subset of participants (ages 2-10) will undergo an EEG session (inclusive of set up and four paradigms: resting state EEG, visual evoked potentials, auditory evoked potentials, complex social event related potentials. Healthy control data will also be collected.

D) Study Site Information (PIs/Mentors)

Boston Children's Hospital (TSC, PTEN, and PMS):

PI – Mustafa Sahin, MD, PhD (Consortium Investigator)

EEG Lead – Chuck Nelson, PhD

MRI Lead – Simon Warfield, PhD

Biostatistician – Bo Zhang, PhD

Stanford University (TSC, PTEN, and PMS):

TSC PI – Brenda Porter, MD

PTEN PI – Antonio Hardan, MD

PMS PI – Jon Bernstein, MD

Cincinnati Children's Hospital Medical Center (TSC and PTEN):

PI – Darcy Krueger, MD, PhD (TSC Study Chair)

PI – David Ritter, MD, PhD

University of California at Los Angeles (TSC and PTEN):

TSC PI – Shafali Jeste, MD

PTEN PI – Julian Martinez, MD, PhD

University of Alabama at Birmingham (TSC):

PI – Martina Bebin, MD

University of Texas Health Science Center at Houston (TSC):

PI – Hope Northrup, MD

Lead TSC Psychologist – Deborah Pearson, PhD

Cleveland Clinic (PTEN):

PI – Charis Eng, MD, PhD (PTEN Study Chair)

Lead PTEN Psychologist – Robyn Busch, PhD

Mount Sinai School of Medicine (PMS):

PI – Alex Kolevzon, MD (PMS Study Chair)

Director of Administrative Core – Joseph Buxbaum, PhD

National Institutes of Health (PMS):

PI and Lead PMS Psychologist – Audrey Thurm, PhD

Rush University Medical Center (PMS):

PI – Elizabeth Berry-Kravis, MD, PhD

PI – Latha Soorya, PhD

Consultant:

Lead Psychologist – Celine Saulnier, PhD