**Symposium Title:** Behavioral Phenotyping: Natural History Data from Genetic Conditions Affecting Neurodevelopment and Testing the Limits of Measures

**Chair:** Cristan Farmer¹ & Audrey Thurm¹

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**Overview:** With the advent of improved diagnostics, identification of genetic conditions affecting neurodevelopment is increasing. The resulting prevalence allows for natural history studies of a variety of genetic conditions less common than those traditionally associated with Intellectual Disability (ID). The studies have converged on common measures of neurodevelopment, using systematic approaches that often call for the use of tests that do not necessarily cover the range of impairments associated with these rare genetic conditions. Here we report four papers that provide new insights into the neurodevelopmental characterization of genetic conditions associated with ID, based on the largest datasets collected to date, and covering a variety of conditions associated with medical conditions (e.g. epilepsy) that complicate behavioral presentations. The goal is to reflect on what we are learning about profiles of cognitive and behavioral functioning from the growing natural history studies of rarer genetic conditions associated with ID, and to critically consider the ways we select and implement neurodevelopmental test batteries. The first paper reports initial findings from a Rare Disease Clinical Research Network project characterizing three genetic conditions affecting neurodevelopment with common etiological pathways relating to compromised synaptic functioning. The neurodevelopmental profiles of these conditions appear quite distinct, with major differences in basic IQ ranges that affect the ability to make differential diagnoses, such as the separation of autism spectrum disorder from ID. The second paper reports on a very rare neurometabolic condition, creatine transport deficiency, that is highly associated with global developmental delays leading to ID. This study uses a new measure of adaptive functioning, and some preliminary longitudinal data will be presented that allow us to begin profiling based on finely tuned measures of developmental trajectories. The third paper reports on 15q11.2-q13.1 (dup15q syndrome), integrating information about type of duplication and epilepsy comorbidity in relation to severity of cognitive impairments, and explores how all of these relate to behavior problems. The fourth paper empirically addresses several measurement issues that arise in these studies of rare genetic disorders associated with ID, including analyses to understand which factors predict when alternative cognitive assessment is appropriate, how cognitive assessments relate to measures of adaptive functioning, and the impact of a new test version on adaptive behavior scores. We will then discuss the meaning of these findings with respect to increasing efforts to understanding behavioral phenotypes as they relate to the natural progression of genetic conditions, as well as our ability to measure change over time.

**Paper Title:** Behavioral Phenotyping of Genetic Disorders Comprising Developmental Synaptopathies: Tuberous Sclerosis Complex, PTEN Hamartoma Tumor Syndrome, and Phelan-Mcdermid Syndrome

**Authors:** Latha Soorya³, Audrey Thurm¹, Cristan Farmer¹, Alexander Kolevzon⁴, Joseph Buxbaum⁴, Elizabeth Berry Kravis³ Craig Powell⁹, Jon A. Bernstein⁶, Charis Eng⁷, Darcy Krueger⁸, Mustafa Sahin⁹ on behalf of the Developmental Synaptopathies Consortium

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Introduction: The Developmental Synaptopathies Consortium includes a group of studies dedicated to collecting parallel and comparative natural history on three genetic conditions associated with intellectual disability (ID) and autism spectrum disorder: tuberous sclerosis complex (TSC), PTEN hamartoma tumor syndrome (PHTS), and Phelan-McDermid Syndrome (PMS). These conditions differ due to their specific genetic alterations, but are neurobiologically similar in that they affect mechanisms related to the development or functioning of synapses. Here, we describe the basic behavioral phenotyping results with respect to IQ and autism symptom profiles.

Methods: The study samples comprised 95 participants in the PMS group (mean age 9 ± 5 years), 83 with TSC (mean age 9 ± 5 years), 34 with PHTS+ASD (mean age 9 ± 5 years), and 20 with PHTS-No ASD (mean age 10 ± 5 years). Participants were administered an assessment battery that included a cognitive test (Mullen, DAS, or Stanford Binet, depending on age/ability, and ratio IQ scores were required for many participants due to floor effects) and an Autism Diagnostic Observation Schedule (ADOS). Descriptive statistics are reported, and the rate of meeting ASD criteria on the ADOS as a function of mental age is evaluated.

Results: A wide range of nonverbal IQ (NVIQ) was observed in each of the groups. The PHTS no ASD group had the highest mean NVIQ (92 ± 25; range 38 – 137), followed by PHTS+ASD (59 ± 25, range 20 – 123), TSC (53 ± 23, range 4–99), and PMS (24 ± 20, range 1 – 83). The percentage of participants who had nonverbal mental age below 18 months was highest for PMS (43%), followed by TSC (13%), PHTS+ASD (6%), and PHTS no ASD (0%). The majority of the PHTS-no ASD group was not administered the ADOS or ADI-R, so is not included in the remaining results. Of the 84 participants with PMS who received an ADOS, 64 (76%) met criteria. In the TSC group, 43 of 77 (56%) met criteria, as did 26 of 32 (81%) in the PHTS+ASD group. In the PMS group, participants with a nonverbal mental age below 18 months were more likely to meet ASD criteria on the ADOS (91% vs. 68%, Fisher’s exact test p = .03). This was also true in the TSC group (100% vs. 48%, Fisher’s exact test p = .0008). Too few PHTS+ASD participants had nonverbal mental age below 18 months to perform the analysis. Within the TSC and PMS groups, an ROC analysis was performed, predicting ADOS classification from NVIQ. The AUC for this model was 82%; the predicted probability of meeting the ASD cutoff decreases linearly between IQs of 25 and 75, but flattens below or above that range. Further analysis will explore the relationship between NVIQ and the ASD consensus diagnosis.

Discussion: These findings describe widely varying ID profiles among the various genetic conditions, with PHTS showing the range of IQ scores that is most preserved, with a mean only falling into the ID range for the subgroup diagnosed with ASD. From this sample, both TSC and PMS can be described as predominately ID conditions, with PMS IQs mostly in the severe-to-profound ID categories. As expected based on prior reports, ASD symptoms were common in all conditions, but these findings indicate that in individuals with a mental age of less than 18 months, ASD symptoms may be conflated with severe-to-profound ID.

Paper 2 of 4

Paper Title: Preliminary Behavioral Phenotyping Results From the First Natural History Study of Creatine Transport Deficiency

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Introduction: Creatine Transport Deficiency (CTD) is a genetic condition associated with neurodevelopmental disorders, based on a rare X-linked gene mutation on SLC6A8 gene. Transport of creatine to the brain is limited. Although there has not yet been a prospective natural history of this condition, retrospective reports indicate many children with this condition experience global developmental delays leading to intellectual disability and epilepsy (van de Kamp et al., 2013). The current study reports initial descriptive data from the first multi-site natural history of the condition. This study includes up-to-date neurodevelopmental

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measures, such as the Vineland Adaptive Behavior Scales, Third Edition (VABS-3), which provides growth scale values, potentially helpful in capturing subtle developmental progress that is difficult to capture in youth with developmental delays.

**Methods:** Eighteen individuals with CTD participated in this study which has extended to 18-month follow-up for the first cohort (age M=6.7, SD=3.4 years, range 3 – 13). The scores included in this analysis were drawn from the VABS-3 and IQ testing (Mullen Scales of Early Learning or Wechsler Abbreviated Scales of Intelligence, depending on the age/ability level of the participant). Both standard scores (SS; which reflect position relative to age-peers) and growth scale values (GSV; which are a unitless index of ability intended to be sensitive to change) were generated from the VABS-3. Ratio IQ and deviation IQs were combined for composite NVIQ and VIQ measures. Baseline VABS and IQ profiles are described. Baseline to 6-month change (n=13) was assessed via contrast statements in a mixed model with an unstructured covariance matrix for residuals. Analysis of the 12-month and 18-month change will also be presented at the meeting.

**Results:** At baseline, the average VIQ (M=33.8, SD=16.7) and NVIQ (M=37.8, SD=12.9) scores were similar; the mean NVIQ-VIQ difference was 4.0 (SD=7.9, range -13 – 16). Participants exhibited a relative deficit in VABS-3 Communication (M=36.9, SD=17.7) compared to Daily Living Skills (M=54.0, SD=14.4) and Socialization (M=48.1, SD=18.3). At 6 months, for IQ and VABS-3, standard scores were stable or decreased slightly (M(SE) change): VIQ, -1.7(1.7), p=.34; NVIQ, -2.2(1.7), p=.23 and VABS-3 ABC, -1.1(2.0), p=.63. While domain standard scores were stable or decreased, the GSV for the VABS-3 generally increased or remained stable. For example, the Daily Living Skills SS decreased slightly [-2.4(2.8), p=.41], while the subdomain GSV increased or remained stable: Personal [+1.5(1.6), p=.37], Domestic [+5.4(1.6), p=.007], and Community [-0.5(2.0), p=.82].

**Discussion:** These results demonstrate the significantly impairing developmental delay/intellectual disability present in youth with CTD evaluated in a natural history study to date. Limited longitudinal data indicate that development is slow, yet not undetectable with measures designed specifically to show progress in skill development within an individual over time.

**References/Citations:**
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**Paper 3 of 4**

**Paper Title:** Developmental and Behavioral Characteristics of Children with Dup15q Syndrome

**Authors:** Charlotte DiStefano², Carly Hyde³, Vidya Saravandipan², Rujuta Wilson² & Shafali Jeste²

**Background:** Duplication of 15q11.2-q13.1 (dup15q syndrome) is one of the most common copy number variations associated with autism spectrum disorders (ASD) and intellectual disability (ID). Its prevalence in the general population is unknown, but may be as high as 1:5000 (Kirov et al., 2014). The Dup15q phenotype is characterized by social communication deficits, ID, language delay, hypotonia, motor delays, and epilepsy (Battaglia, Parrini & Tancredi, 2010). As with many neurogenetic conditions, gathering accurate developmental and behavioral assessments is challenging, due to the level of impairment and heterogeneity of the population. Large-scale phenotyping studies are necessary to inform participant selection and clinical endpoints for future clinical trials.

**Objectives:** The purpose of this study was to systematically assess developmental and behavioral characteristics in a large cohort of children with dup15q syndrome, as a basis for future clinical trials for this and similar syndromes. Our specific aims were to 1) Identify differences based on presumed gene dosage (duplication type), 2) Identify differences based on epilepsy status, and 3) Evaluate the value of various standardized assessment tools for characterizing and stratifying participants.
Methods: Participants included 60 children with dup15q syndrome ages 30 months – 18 years, recruited from the national Dup15q Alliance and the UCLA Dup15q clinic. We evaluated multiple domains of development through both direct assessment and parent report, and we examined overall group phenotype as well as profiles based on duplication type and epilepsy status. Given that many children perform at or near the floor of most standardized assessments, we used a flexible set of cognitive assessments and computed ratio scores using age equivalent scores and chronological age.

Results: Both duplication type (int(15), idic(15)) and epilepsy had a large impact on development across cognitive, language, motor and adaptive domains. Children with idic(15) and epilepsy showed the greatest level of impairment, while children with int(15) duplications showed the least. Additionally, parents reported more elevated concerns regarding other behavior problems in children with idic(15). Across all participants, there was a wide range of abilities. Three participants had DQ scores in the average range, while the remaining participants scored in the mild to severely impaired range. Adaptive behavior (VABS) scores were significantly different across domains (F=14.69, p<.001). Communication domain scores were significantly lower than socialization (t=4.69, p<.001) and motor domains (t=3.18, p=.003), while daily living skills domain scores were significantly lower than socialization (t=3.19, p=.002) and motor domains (t=2.32, p=.03). Although adaptive behavior was strongly associated with cognitive ability, VABS scores were higher on average than cognitive scores (t=11.73, p<.001). Measures of social communication were highly associated with DQ, while parent report of challenging behavior (Aberrant Behavior Checklist) was not.

Conclusions: By using a comprehensive and flexible set of assessments, we were able to gather meaningful information on the developmental and behavioral characteristics of a large and diverse group of children with dup15q syndrome. Findings confirmed that both duplication type and epilepsy likely contribute to the level of impairment observed, although there is still substantial heterogeneity across individuals. Clinical trials in ID syndromes should employ a flexible set of assessments, that allow each participant to receive the assessment that is the best fit for their skills. When assessing other domains of behavior, multiple sources of information should be considered (both direct observation and parent report), and the impact of language and cognitive ability should be taken into consideration when interpreting results.

Paper 4 of 4

Paper Title: Empirical Evaluation of Common Methods for the Measurement of IQ and Adaptive Behavior in Trials with Rare Genetic Conditions

Authors: Cristan Farmer1, Vanessa Bal1, Audrey Thurm1, Colby Chlebowski1

Introduction: Assessment with standardized scales is difficult in individuals with moderate-to-severe intellectual disability (ID), due to floor effects. Given the elevated rate of ID among individuals with genetic disorders, researchers who study rare genetic conditions frequently contend with the tension between maintaining standardization on a given instrument and obtaining the data necessary for a study. In this presentation, we will describe results from several research projects converging on the methodology of measuring IQ and adaptive behavior in trials with rare genetic conditions.

Methods: We utilized a database comprised of research evaluations performed in natural history and intervention trials in several conditions associated with neurodevelopmental sequelae. All individuals evaluated by our group receive the same battery, including the Vineland Scales of Adaptive Behavior (second, third, or both editions) and a cognitive test (Mullen Scales of Early Learning, Differential Abilities Scale II), which are the focus of the current presentation. Subsets of the database were used to answer the following research questions: (a) What rules do clinicians use to decide whether to perform an out-of-age-range IQ test (analytic approach: classification trees); (b) Is the Vineland Adaptive Behavior Composite a reasonable substitute for IQ (analytic approach: mixed effects model); and (c) What is the correspondence between the recently-released Vineland-3 and the Vineland-II (analytic approach: mixed effects model)?

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Results: For the first question, a subset of 241 participants was split into training and testing datasets for cross-validation. A decision tree was computed, using age equivalents from the Vineland-II, age, and sex as predictors of whether the child received the Mullen (out-of-age-range; n=54 participants) or received the DAS. The best model used Vineland-II Fine Motor (<48 months), Play Time (<16 months), and Receptive Language (<30 months) to predict a Mullen administration with 90% accuracy. For the second question, a random effect model predicting NVIQ from 1,780 Vineland-II ABC scores from 986 individuals demonstrated a strong linear relationship ($B_{NVIQ} = 1.25(0.03)$, $p < .0001$), but significantly higher ABC scores at lower levels of IQ (i.e., the model-estimated difference between ABC and NVIQ ($\Delta$) was 0 for NVIQ=90, $\Delta = 5$ for NVIQ=70, $\Delta = 10$ for NVIQ = 50, and $\Delta = 15$ for NVIQ=30). Finally, we evaluated the relationship between contemporaneously administered Vineland-II and Vineland-3 in 97 individuals. ABC scores from the two versions were almost perfectly correlated ($B = 0.97(0.04), p<.0001$). However, the mean Vineland-3 ABC score was approximately 8 points lower than the Vineland-II score (data centered at 100; intercept = -8.40(1.64), $p < .0001$). Seven (31%) participants with Vineland-II scores above 70 had Vineland-3 scores less than 70 while three (3%) had Vineland-II scores less than 70 and Vineland-3 above 70.

Discussion: These results demonstrate that information gathered from a caregiver, such as Vineland ratings, may be used in a systematic manner to guide decisions about using an out-of-level test in an individual moderate-to-profound ID. The importance of systematic decision making in this respect is underscored by the fact that it may have a significant impact on estimation of IQ. Our previously published work demonstrated a significant difference in IQs estimated by the DAS and MSEL, and here we found that the Vineland-II ABC overestimates NVIQ more dramatically among individuals who are unlikely to achieve basal on age-appropriate tests. Of note, the recently released Vineland-3 may be a better substitute for IQ than the Vineland-II, as improvements were made to measurement at the lower levels of ability. Indeed, the results described here indicate that while Vineland II and Vineland-3 scores are strongly correlated, Vineland-3 scores tend to be lower and may reflect a more accurate assessment of adaptive functioning in individuals with moderate-to-profound ID.