2026 PMSF Family Conference Poster Abstracts

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1. **Title: Behavioral phenotypes and neuronal biomarkers in F1 mutant macaque model of SHANK3-associated autism spectrum disorders**

Presenter: Minqing Jiang
Authors: Minqing Jiang*, Ronghui Li*, Xing Yang*, Zhen Ren*, Zijiang Yang*, Frederico Azevedo*, Jitendra Sharma, William Menegas, Lixin Yang, Ji Dai, Liping Wang#, Shihua Yang#, Robert Desimone#, Guoping Feng#, Zhonghua Lu#
Affiliations: McGovern Institute for Brain Research at MIT; Yang-Tan collective Shenzhen Institute of Advanced Technology, Chinese Academy of Science
Abstract: Haploinsufficiency of the SHANK3 gene is the primary cause of Phelan-McDermid syndrome (PMS), a severe neurodevelopmental disorder with intellectual disability and autism spectrum disorder. We previously reported that founder SHANK3 macaques had behaviors reminiscent of some aspects of PMS. However, insights into behavioral, physiological and cognitive changes were limited due to the small cohort and mosaicism. We therefore generated a larger, F1 generation of heterozygous SHANK3+/- macaques to conduct more thorough studies. We found sleep disturbances, diminished exploration, atypical social interactions, stereotypical behaviors and altered brain functional connectivity in SHANK3+/- macaques. Electroencephalogram recordings revealed a markedly diminished response to auditory stimulation. Cognitively, SHANK3+/- monkeys did not show major deficits in working memory tests but exhibited an impaired ability to learn and execute a paired-association memory task. We further developed a multi-task array to systemically evaluate autism-related phenotypes, which revealed the heterogeneity of phenotypes and established potential biomarkers for testing therapeutics.

2. **Title: Energetic and Ribosomal Pathway Changes in the Gut of a Shank3 Zebrafish Model of Phelan-McDermid Syndrome**

Presenter: Lidia Garcia-Pradas
Authors: Lidia Garcia-Pradas[1], Adhikansh Jain[1], Lianet Jimenez[1], Julia Dallman[1]
Affiliation: University of Miami
Abstract: Background: Phelan-McDermid syndrome (PMS), caused by SHANK3 haploinsufficiency, is frequently accompanied by gastrointestinal disturbances, including constipation, diarrhea, reflux, and cyclical vomiting, yet the mechanisms underlying these symptoms remain unclear. In the shank3abΔC zebrafish model, larvae display delayed intestinal transit. Previous analyses in this model also identified fewer serotonin-producing enteroendocrine cells (EECs), and preliminary assays suggest altered nutrient-sensing responses in mutants. These observations suggested that broader cellular programs might be altered, leading us to perform bulk RNA sequencing of dissected gut tissue. Methods: Guts were dissected from 6 days post-fertilization wild-type and shank3abΔC+/- larvae (25-30 guts per sample; n=3 per genotype). Total RNA was extracted and subjected to poly(A)+ bulk RNA sequencing. Differential expression was analyzed using DESeq2 (padj < 0.05), followed by Gene Ontology enrichment analysis. To assess whether transcriptional

changes translate to altered protein production, O-propargyl-puromycin (OPP) labeling experiments are in progress. Results: Mutant gut tissue shows reduced expression of multiple ribosomal genes as well as components of mitochondrial oxidative phosphorylation pathways. Enrichment analyses highlight processes related to translation, mitochondrial activity, and ATP metabolism, indicating shifts in gene programs that support cellular energy production. Discussion: These findings suggest that Shank3 deficiency is associated with broad transcriptional changes in pathways linked to energetics within gut tissue. Ongoing protein synthesis assays will help determine whether these molecular signatures correspond to functional differences. Understanding how altered energetic state affects gut signaling may provide insight into gastrointestinal symptoms in PMS.

3. **Title: Mutations of Autism-linked genes drive shared perceptual deficits across species**

Presenter: Amanda B. Fath
Authors: A. B. Fath[1,2], U. Mishra[5], C. Delgado-Sallent[5], A. Khawaja-Lopez[5], S. Chakravarty[5], W. Menegas[3,4], G. Feng[1,2,3,4*], B. B. Scott[5*]
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Abstract: Atypical sensory processing is a hallmark of autism spectrum disorder (ASD) and strongly predicts other core symptoms. However, the underlying computational and neural mechanisms remain poorly understood, in part due to the difficulty of modeling complex ASD symptoms in animals. Synchronized cross-species tasks provide a unique opportunity to quantitatively compare symptomatology in humans with autism and corresponding animal models. Here we use a recently developed cross-species sensory integration task across humans, mice, and marmosets to study perceptual deficits associated with Shank3 mutations, which underlie Phelan-McDermid syndrome (PMS). The human cohort spanned the autism spectrum, including individuals with PMS, and was complemented by parallel studies in Shank3 mutant and wild-type (WT) mice and marmosets. High-throughput behavior acquisition allowed for the generation of a large dataset (136 humans, 66 mice and 46 marmosets), and the task was playable across all species and groups, including humans with more severe ASD, such as PMS. Quantitative comparison indicated similar deficits in perception and learning, across humans, mice and marmosets with Shank3 mutations. Drift diffusion model (DDM) analysis revealed that these deficits are due to a decrease in drift rate, consistent with altered perceptual integration. In humans, gameplay statistics including drift rate, correlated with clinically relevant symptoms, assessed by traditional survey scores. Together these data indicate that Shank3 mutant mice and marmosets mimic specific perceptual deficits found in ASD and highlight the value of cross-species tasks for translational research and the discovery of disease mechanisms.

4. **Title: Inflammation increases the penetrance of behavioral impairment in Shank3 haploinsufficiency mice — can it explain the behavioral regression in Autism?**

Presenter: Sheng-Nan Qiao
Authors: Sheng-Nan Qiao[1], Sung Eun Wang[1], Kun-Yong Kim[1], Sungsin Jo[2] and Yong-hui Jiang[1]
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Abstract: Behavioral regression occurs in approximately 40% of individuals with SHANK3-associated autism spectrum disorder (ASD). We previously reported that significant behavioral regression in a small cohort of patients with SHANK3 haploinsufficiency, triggered by
subclinical infections, responded to immunomodulator treatments. We hypothesize that behavioral regression results from the interplay between SHANK3 deficiency and neuroinflammation. Using Shank3 exon 4–22 deletion heterozygous mutant (Sh3+/−) mouse, which shows no significant behavior impairments, we established a preclinical model – Shank3 haploinsufficiency mouse undergoing a systemic inflammation challenge via intraperitoneal injection of lipopolysaccharides (LPS). We found that, two weeks after LPS challenge, wild-type mice (WT) recovered but Sh3+/− mice exhibited motor impairment, anxiety-like behaviors, and excessive grooming, similar to Shank3 exon 4–22 deletion homozygous mutants. Anti-inflammatory treatment partially reversed LPS-induced behavioral changes. Transcriptomic analysis revealed upregulation of neuroinflammation-related genes and downregulation of synaptic function-related genes in LPS challenged Sh3+/− mice. Especially, pro-inflammatory genes and microglia markers were overly activated that may result from the increased toll-like receptor 4 (TLR4) in Sh3+/− mice. Microglia overactivation elevated synapse engulfment and disrupted synaptic protein may underlie LPS-triggered worsen behavior phenotypes in Sh3+/− mice. Together, our findings indicate that neuroinflammation increases the penetrance of behavioral impairment in Shank3 haploinsufficiency mice and support a potential mechanism for the behavioral regression in human SHANK3 related disorders for future investigations.

5. **Title: Phelan-McDermid Syndrome Research Initiative (PMS-RI) at Clemson University: updates and current projects.**

Presenter: Luigi Boccuto
Authors: Luigi Boccuto[1], Sara M. Sarasua[1], Bridgette A. Moffitt[1], Katherine E. Weisensee[2], Diana Ivankovic[1], Emily Payne[1], Sarah Valverde[1], Ethan Wilson[1], Jillian Spencer[1], Sydney Clark[1], Anika Vercateuren[1], Audrey Bowlds[1], Giuseppe G. M. Scarlata[3], Ludovico Abenavoli[3], Curtis Rogers[5], Katy Phelan[6], Zoe Vickery[1], Ben Farabee[1], Prasamsa Tatinemi[1], Jessica Odenwood[1], Sydney McCune[1], Reagan Nelson[1], Lola Hakimi[1].
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Abstract: Background: Genotype-phenotype correlations are instrumental in understanding the pathogenic mechanisms underlying the clinical presentation of Phelan-McDermid syndrome (PMS) and identifying molecular targets for treatment strategies. The PMS Research Initiative (PMS-RI) at Clemson University investigates the clinical, genetic, and functional features of PMS and develops precise strategies to treat them. Recently completed projects: Speech/language impairments and their correlations with 22q13 deletion size or SHANK3 variants, Clinical, genetic, and metabolomic profiles of individuals with behavioral abnormalities, Three-dimension (3D) morphometric assessment to investigate craniofacial dysmorphisms, Clinical and metabolomic features in a longitudinal study of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in PMS, Assessment of the in vitro metabolic response to candidate compounds (IGF-1, hGH, insulin, lithium, zinc). Methods: The clinical assessments employed standardized methods, such as ADI-R and Vineland III, for the behavioral abnormalities. The 3-D craniofacial landmarks and semi-landmarks were analyzed in MorphoJ using Principal Component Analysis (PCA), Procrustes MANOVA, and Canonical Variates Analysis (CVA). The metabolomic profiles for functional studies and in vitro assessment of candidate compounds were generated using the Biolog Phenotype Mammalian Microarray (PM-M) technology. Results: SHANK3 alterations play a prominent role in speech/language delay and behavioral abnormalities. The 3-D morphometric assessment identified recurrent craniofacial features in the PMS population. MASLD should be considered as a potential long-term complication in individuals with large 22q13 deletions encompassing the PNPLA3 gene. The metabolomic profiling stratified the PMS population according to high and low energetic responses to candidate compounds and revealed the most affected pathways.
Discussion: Metabolomic profiling is a promising strategy for preclinical identification of ideal candidate subjects for trials and monitoring adverse effects. Clemson University has a sustained research program in PMS with over 18 publications and welcomes opportunities for collaboration to improve care for people with PMS.

6. **Title: Secondary genomic abnormalities contribute to atypical phenotypes in Phelan-McDermid Syndrome**

Presenter: Andres Jimenez-Gomez
Authors: Andres Jimenez-Gomez, MD[1], Adanze Nnyagu MD[1], Mikael Guzman-Karlsson, MD PhD[1], Lisa Emrick, MD[1], Holly Harris MD[2], Jimmy Holder Jr MD PhD[1]
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Abstract: Background: Due to genetic heterogeneity, Phelan-McDermid Syndrome (PMS) exhibits variable clinical presentation, particularly in severity of developmental and behavioral phenotypes. However, even when accounting for this variability, some individuals fall outside the expected phenotypic spectrum of PMS. This may be explained by a secondary genetic lesion, which may result in blended phenotypes, altered severity of the primary phenotype, or phenotypes not clearly attributable to either lesion. We evaluated the prevalence of secondary lesions, and atypical phenotypes, in a cohort of individuals with PMS. Methods: Clinical records from all individuals diagnosed with PMS at a single institution were retrospectively reviewed.

Phenotypic traits were reviewed to identify trajectories atypical for PMS, as well as novel neurologic and non-neurologic comorbidities. Genetic testing results were reviewed to identify primary and secondary genetic abnormalities and their possible role in the phenotype. Results: Seventy-three individuals with PMS and available genetic results were included (71% deletion, 29% pathogenic variants). Thirteen possible secondary genetic findings were seen in 12 individuals, with two additional having clinical findings meeting criteria for additional genetic conditions. Secondary findings were hypothesized to worsen the phenotype of 5/14 individuals (variants in IMMP2L, LRRTM4, DOCK8 duplication, 15q13.3 microduplication). 8/14 were suspected to have independent phenotypes driven by the secondary finding, affecting multiple other organ systems (Ring chromosome resulting in NF2[JH1.1], deletion in ARSA; variants in TYMP, NYX, APOB, FLG, and TXNB). Overall, 9/12 identified genes/loci are not contiguous with the primary genetic locus (22q13). Discussion: Clinical findings that fall outside the expected PMS phenotype should prompt additional genetic testing, including other modalities. In individuals with terminal deletions, evaluation for ring chromosome and, independently, possible imaging to rule out NF2 is necessary. Genetic testing with more comprehensive modalities should become standard of care for evaluation of individuals with PMS and may offer additional information for preventive screening and surveillance.

7. **Title: Building a Co-Located, Same-Room Interdisciplinary Clinic for Phelan McDermid Syndrome at Cincinnati Children's Hospital**

Presenter: Amelle Shillington
Authors: Amelle Shillington, DO, Rachel Doberstein MS, LGC, David Franz, MD, Theodore Vanover, RN, Kelli Dominick MD, PhD
Affiliations: Cincinnati Children's Hospital
Abstract: Phelan-McDermid syndrome is a complex, multisystem neurodevelopmental disorder affecting neurologic, medical, behavioral, and developmental domains across the lifespan. Consensus guidelines call for coordinated, multidisciplinary care, yet most families still navigate separate referrals, separate visits, and separate clinical notes. Families travel long distances and take multiple days off work and school to see neurology, genetics, GI, psychiatry, developmental pediatrics, and therapy teams, on different days, often in different buildings. In rare-disease clinics, this fragmentation, not lack of expertise, is consistently named as the main source of caregiver burden and missed coordination. At the Cincinnati Children's Phelan-McDermid Syndrome Clinic, every core provider sees the family together, in one room, during one scheduled visit. The team builds the plan together, with the family present. Neurology, Genetics, and Psychiatry providers co-locate in the same exam room, in the same appointment and build the care plan together with the family present.

8. **Title: Challenging Behavior Profiles in Children with Co-Occurring IDD and PMS or FXS: A Multi-Method Approach to Inform Intervention Targets**

Presenter: Haley Zeri
Authors: Haley Zeri[1], Jason Cano[1], Edith Ocampo[1], Noah Torres[1], Niramay Patel[1], Madison Nava[1], Nathan Call[2], Joanna L. Mevers[2], Jennifer M. Hodnett[2], Lawerence Scahill[2], Elizabeth Berry-Kravis[1], Allison Wainer[1], Latha Valluripalli Soorya[1]

Affiliations: 1. Rush University Medical Center, Chicago, IL, 2. Emory University, Atlanta, GA

Abstract: Background: This study seeks to inform understanding of challenging behaviors in children, ages 2-12 years old, with PMS or FXS. Specifically, we evaluate profiles of challenging behaviors from a standardized checklist, Behavior Problems Inventory (BPI-01) and caregiver-reports of top problems designed to inform intervention targets on the Parent Target Problems (PTP), an open-ended interview. Methods: 23 caregivers (86.96% female) of eligible participants with PMS (n = 12) or FXS (n = 11) and co-occurring IDD (Male = 69.57%; Mild = 47.83%, Moderate = 34.78%, Severe = 17.39%) aged 2-12 years (M = 7.65, SD = 3.19) completed the PTP and BPI-01 according to established trial protocols (NCT06139172). We calculated the percentage of caregivers endorsing behaviors related to Aggression, Stereotypies, Self-Injury-three topographies captured in both the PTP and BPI-01. Results: Aggression and Compliance Issues were among the top PTP concerns for PMS and FXS caregivers. Aggression was endorsed similarly across groups on the PTP (PMS: 58.33%; FXS: 45.45%) and BPI-01 (PMS: 66.67%; FXS: 54.54%). Self-Injury was endorsed as occurring at high rates in PMS (75%) with higher levels than FXS (54.54%) on the BPI-1 checklist. In contrast, parents in both conditions were less likely to identify Self-Injury as a top target problem on the PTP (PMS: 8.33%, FXS: 18.18%). Similarly, on the BPI-1 Stereotypy was the most frequently endorsed behavioral challenge across PMS (91.67%) and FXS (81.81%), however, it was not selected for intervention targets by parents on the PTP. Discussion: In this study, Self-Injury and Stereotypy were less likely to be endorsed as intervention targets but occur at high rates in both PMS and FXS children. Differences in characterization of challenging behavior profiles on the PTP and BPI-01 highlight the importance of using multi-method approaches that balance characterization (e.g., type, frequency) from intervention targets. Notably, Self-Injury and Stereotypy are more often associated with sensory-seeking and self-soothing functions than Aggression suggesting a need to understand the relationship between behavior function and selection of intervention targets.

9. **Title: Exploring Relationships Between Sensory and Challenging Behavior Profiles in Children with PMS**

Presenter: Jason Cano

Authors: Jason Cano, Haley Zeri, Edith Ocampo, Noah Torres, Niramay Patel, Madison Nava, Elizabeth Berry-Kravis, Allison Wainer, Latha Valluripalli Soorya

Affiliations: Rush University Medical Center

Abstract: Introduction: This study explores relationships between sensory profiles and challenging behaviors in children, ages 2-12 years old with Phelan-McDermid Syndrome (PMS) participating in a behavioral intervention trial. Specifically, we seek to categorize sensory profiles using the Sensory Assessment for Neurodevelopmental Disabilities (SAND) and examine relationships between sensory profiles and challenging behaviors on the Behavior Problems Inventory (BPI-01). Method: 12 caregivers (Female = 83.33%) of participants with PMS (Male = 66.67%) received the SAND and BPI-01 according to established the trial protocol (NCT06139172). We calculated means SAND subtype scores (Hyperreactivity, Hyporeactivity, Sensory-Seeking) and frequency of challenging behavior categories from the BPI-01 (Aggression, Self-Injury, Stereotypy). Spearman's rank correlation was used for correlational analysis. Results: The mean SAND total score was 17.58 (SD = 7.15).

Descriptive data suggest Sensory Seeking (M = 6.91) was rated the highest in this sample, followed by Hyporeactivity (M = 5.91), and then Hyperreactivity (M = 4.75). Correlational analyses indicate Sensory Seeking and Stereotypy are positively and significantly correlated (r = 0.80, p = 0.0016). Hyporeactivity and Aggression are also positively and significantly correlated (r = 0.75, p = 0.0049). Discussion: Results on sensory profiles in PMS replicate prior studies finding higher Sensory Seeking and Hyporeactivity relative to other domains. Sensory Seeking had positive association with stereotyped behaviors, suggesting potential positive/reinforcing functions across these domains. The association between Hyperreactivity and Aggression is particularly significant given the potential for this finding to suggest aggression in may be less socially motivated and socially driven than other populations. Together, findings provide several potential avenues to understand biological and functional relationships between sensory processing and behavioral challenges in PMS.

10. Title: Auditory processing disruptions in Phelan-McDermid Syndrome reflect altered gamma-band activity

Presenter: Jordan Norris*, Presented by: Tara Khandelwal
Authors: Jordan E. Norris[1,2], Lauren M. Schmitt[3], Stephen Elliott[4,5], Kimberly Goodspeed[6], & Lauren E. Ethridge[1,7]
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Abstract: Phelan-McDermid syndrome (PMS), caused by a mutation in SHANK3 leading to haploinsufficiency of the protein product (SHANK3). Loss of SHANK3 alters the excitatory/inhibitory balance and alters sensory processing, frequently evidence in PMS electroencephalography (EEG) studies. To date, limited studies have characterized auditory responses in adolescents and adults with PMS using EEG. Thus, the present study aims to address this gap. Participants were N = 9 individuals with PMS (6 female) and N = 9 typically developing controls (TDC; 5 female) between 11 and 28 years of age (PMS: M = 18.56, SD = 4.83; TDC: M = 17.33, SD = 4.15) who completed an auditory chirp task. Time-frequency analyses evaluated intertrial phase coherence (ITC) and event-related spectral perturbation (ERSP) across the chirp range to assess temporal precision of auditory responses and evoked power, respectively. Low gamma ITC (30-62 Hz) was significantly reduced in PMS relative to TDC (z = -3.12, p = .001) and gamma ERSP was increased in PMS across the full frequency range (low gamma [30-65 Hz]: z = 2.25, p = .024; high gamma [66-110 Hz]: z = 2.25, p = .024; upper high gamma [90-110 Hz]: z = 2.34, p = .019). Reduced low gamma (40 Hz) ITC in individuals with PMS reflects temporal imprecision in neural entrainment, consistent with impaired network synchrony observed in other rare single-gene disorders and associated with broadened auditory tuning and altered inhibitory control. Whereas elevated upper high gamma (90–110 Hz) ERSP indicates increased local excitatory population activity, suggesting a shift toward high-frequency power that reflects altered cortical excitability. In conclusion, these

findings demonstrate that individuals with PMS exhibit auditory temporal imprecision alongside elevated excitatory drive that may reflect dyssynchronous background activity, consistent with SHANK3-related cortical dysfunction.

11. **Title: Caregiver Perspectives on Gastrointestinal Survey Instruments in Pediatric Neurodevelopmental Disorders: A Qualitative Analysis**

Presenter: Joseph Termini
Authors: Joseph Termini, BS, Heidi Grabenstatter, PhD, Alycia Halladay, PhD, Katie Madgett, BS, Stacey Keller, MSN, Luigi Boccuto, MD, Lauren Schmitt, PhD, Megan O'Boyle, BA, William E. Bennett Jr., MD, MS
Affiliations: Indiana University, University of Colorado, Autism Science Foundation, Clemson University, Phelan-McDermid Syndrome Foundation
Abstract: Individuals with neurodevelopmental disorders (NDDs), including those with rare genetic syndromes, experience a disproportionately high burden of gastrointestinal (GI) symptoms. Existing patient-reported outcome measures and quality of life instruments, including the GI scale of the Patient Reported Outcomes Measurement Information System (PROMIS), were designed primarily for neurotypical, verbally communicative populations and may be inadequate for capturing the lived experience of nonspeaking or profoundly cognitively impaired children with NDDs. This qualitative study examines caregiver perspectives on the limitations of current GI survey instruments administered during the pre-conference survey of the Consortium for Autism, Neurodevelopmental Disorders, and Digestive Diseases (CANDID) inaugural conference. The findings inform the development of a new, NDD-adapted patient-centered outcome measure (PCOM) for this population. Verbatim free-text caregiver feedback (n=19) collected via a REDCap electronic survey was analyzed using a framework approach to thematic analysis consistent with CDC qualitative research standards. Feedback was inductively coded into refined themes, and a respondent-level matrix was constructed to assess theme frequency and co-occurrence. Nine themes were identified. Universal endorsement (100%) was observed for Instrument Limitations and Severity Undercapture (T1). The most prevalent secondary theme was Exclusion of Rare, Nonverbal, and Low-Functioning Populations (T5; 73.7%, n=14), followed by Physical and Chronic GI Symptom Burden (T2; 47.4%, n=9) and Need for Open-Ended and Caregiver-Narrative Capture (T8; 42.1%, n=8). Existing GI outcome measures are systematically inadequate for children with NDDs, particularly those who are nonspeaking or tube-fed. A co-designed, NDD-specific instrument is urgently needed.

12. **Title: Baseline Gastrointestinal Health in a Pilot Blue-Dye Motility Study of Phelan-McDermid Syndrome**

Presenter: Calliope Holingue
Authors: Calliope Holingue[1,2], William Bennett[3], Barbara Millet[4], Dylan Baker[5], Stacy Anne Keller[3], Andres Jimenez-Gomez[6], Baha Moshiree[7], Julia Dallman[4]
Affiliations: 1. Kennedy Krieger Institute, 2. Johns Hopkins Bloomberg School of Public Health, 3. Indiana University, 4. University of Miami, 5. Symplify LLC, 6. Baylor College of Medicine, 7. Wake Forest University
Abstract: Background: Gastrointestinal (GI) dysfunction is highly prevalent in individuals with Phelan-McDermid syndrome (PMS), yet objective, scalable approaches to characterize gut motility remain limited. We are piloting a

non-invasive method in which participants ingest a standardized blue-colored muffin to estimate whole-gut transit time. This report describes baseline health and GI symptom profiles of enrolled participants. Methods: Participants were 43 parents of individuals with PMS (mean age 17.2 years, SD 11.3; range 4–50) who consented to the motility study. Parents rated their child's GI health, non-GI physical health, mental/emotional health, overall health, and overall quality of life (QOL) over the past month using 0–100 scales (0 = worst possible; 100 = best possible). They also reported frequency of GI symptoms during the prior three months (never to always). Results: Mean parent-rated GI health was 49.9 (SD 26.6), lower than non-GI physical health (64.9, SD 20.6), overall health (60.0, SD 23.3), and overall QOL (65.1, SD 24.0). Mental/emotional health averaged 53.6 (SD 23.7). Symptom burden was substantial. Constipation was reported often or always in 47% of participants and at least sometimes in 81%. Alternating constipation and diarrhea occurred at least sometimes in 43%. Abdominal pain was reported often or always in 18% and sometimes in 21%, though 50% of parents were unsure about its occurrence. Similar variability was observed across other GI symptoms. Discussion: GI health was rated meaningfully lower than other domains, with constipation-related symptoms particularly prominent. Wide dispersion in ratings and high rates of intermittent symptoms highlight the clinical heterogeneity of PMS and the need for objective motility assessment. Parent uncertainty regarding symptoms such as abdominal pain underscores challenges in detection in neurodevelopmental conditions. These findings support integrating standardized, observable measures, including blue-dye–based transit estimation, to complement caregiver reports and improve phenotypic characterization.

13. **Title: STRiPES Symptom Tracker: development of a caregiver-assisted way to track how gastrointestinal and related symptoms vary over time in people with Phelan-McDermid Syndrome.**

Presenter: Julia Dallman
Authors: Dylan R. Baker[1], Paulina Fiore[2], William Bennett Jr.[3], Shamaila Waseem[3], Andres Jimenez-Gomez[4], Robert C. Stowe[5], Baha Moshiree[6], Julia E. Dallman[7], Calliope Holingue[8,9], and Barbara Millet[2].
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Abstract: Background: As part of a PMSF-funded study, we developed the STRiPES symptom tracker mobile application. Our goal was to make a caregiver-friendly tool that could be used to track clinically-relevant gastrointestinal and related symptoms prospectively. Methods: We conducted two rounds of structured usability testing of the STRiPES Symptom Tracker with caregivers, followed by redesigns of the user interface. In addition to consulting with families, to make the tracking clinically relevant, our team included clinicians who regularly care for people with NDDs. After these rounds of refinement, PMS caregivers were recruited to conduct the blue

muffin transit assessment and track symptoms for a month. Results: The usability testing identified key interface challenges and unmet community needs; these insights informed both and the refinement of onboarding questions related to gastrointestinal and medical histories which were used in our research study. For example, PMS caregivers told us that retrospective questions about symptoms could be difficult to answer due to variability in symptoms, so our onboarding questions added an "unsure" option. Twenty-nine caregivers created accounts in the STRiPES Symptom Tracker and logged symptoms for one month or longer (median entries 64; IQR 14.5–124). The most frequently recorded data included bowel movements and mealtimes, while adverse symptoms such as pain, sleep disturbances, and aggression, toward self or others, were more intermittent. Discussion: A key future direction is to leverage these data to better characterize interactions among GI symptoms, with the goal of improving management strategies and quality of life. Ongoing work includes additional usability testing and focus groups with GRIN2B caregivers. The application is currently being adapted to better support individuals who are tube-fed and those with seizures as a tracked symptom domain. We will continue to engage with stakeholders to refine the STRiPES Symptom Tracker and optimize its utility for NDD communities.

14. Title: Characterizing Multimodal Communication in Phelan-McDermid Syndrome Using a Remote Communication Sampling Protocol

Presenter: Kristina T. Johnson
Authors: Kristina T. Johnson[1], Lauren Thompson[2]
Affiliations: Northeastern University, Washington State University
Abstract: Background: Many individuals with Phelan-McDermid syndrome (PMS) are non- or minimally speaking, making it difficult for clinicians and researchers to measure communication using traditional language assessments. Standard tools often rely heavily on verbal speech and may miss meaningful communication expressed through gestures, vocalizations, facial expressions, body movements, or augmentative and alternative communication (AAC). To address this gap, we developed the Rapid Online Sample of Communication (ROSCO), a brief, remote protocol designed to capture naturalistic communication in individuals with complex communication profiles. Methods: ROSCO is a 15-minute semi-structured communication sample conducted over Zoom with caregiver participation. Sessions are followed by a structured caregiver interview to contextualize observed behaviors. Communication samples were coded using the Communication and Symbolic Behavior Scales (CSBS) communicative act framework and compared with caregiver-reported observations and standardized measures, including the Vineland Adaptive Behavior Scales (VABS-3) and the Observer Reported Communication Ability (ORCA) questionnaire. Results: Across coded sessions, participants produced highly variable but clearly intentional communicative acts, with gestures representing the most common communication modality. Contact-based gestures (e.g., touch, give, push away) accounted for a large proportion of communicative behaviors, highlighting the importance of recognizing physical interaction and object transfer as meaningful communication. Caregiver interview data showed strong agreement with CSBS-derived coding for communicative functions, particularly commenting and social interaction. Additionally, vocalization frequency during ROSCO showed positive associations with communication scores on the

VABS-3, while gesture frequency showed weaker or inverse relationships, suggesting that commonly used adaptive behavior measures may underrepresent nonverbal communication modalities.

15. **Title: Profiling Responses and Immune Signatures in SHANK3-Mediated Neuropsychiatric Disease**

Presenter: Jonathan D. Santoro
Authors: Jonathan D. Santoro, Samuel T. Otey, Maeve C. Lucas, Mariam M. Yousuf, Stella V. Gray, Madeline Osborn
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Abstract: Background: Phelan-McDermid Syndrome (PMS) is a genetic disorder resulting from SHANK3 haploinsufficiency. Some individuals with PMS develop neuropsychiatric disease, frequently presenting with subacute neurological regression, mood and behavioral disturbances, and functional decline. The underlying etiology of PMS-associated neuropsychiatric disease (PMS-ND) remains unclear. However, prior clinical responses to various immunotherapeutic interventions suggest a potential role of immune dysregulation. Objectives: This study aims to identify diagnostic biomarkers in individuals with PMS who present with neuropsychiatric disease. Specifically, the research investigates: Whether these individuals possess distinct neurodiagnostic study abnormalities. If patients exhibit unique cytokine, proteomic, and metabolomic profiles in the serum and cerebrospinal fluid (CSF) indicative of systemic and/or central inflammation. Whether specific biomarker patterns can predict disease severity and/or subsequent clinical response to immunotherapy. Methods: This study evaluates a prospective cohort of 30 individuals diagnosed with PMS-ND. Participants undergo standard-of-care neurodiagnostic evaluations, including a clinical routine EEG, brain MRI, and a lumbar puncture for CSF analysis. Biomarker profiling includes measuring cytokines via multiplex immunoassays. Proteomic and metabolomic analyses of plasma and CSF are conducted using mass spectrometry. Disease severity is comprehensively assessed utilizing the Bush-Francis Catatonia Rating Scale (BFCRS) and the Neuropsychiatric Inventory Questionnaire (NPI-Q). Therapeutic responsiveness is evaluated by measuring symptom improvement on the BFCRS or NPI-Q after 6 months of standard-of-care immunotherapy. Significance: This represents the largest prospective cohort of individuals with PMS-ND to date. By generating integrated data sets that track longitudinal outcomes, this study will help determine the highest yield diagnostic studies for PMS-ND. Ultimately, these findings may provide critical insight into the underlying mechanisms of the disease and guide the development of targeted therapeutic strategies.

16. **Title: Serious Neuropsychiatric Illness in Phelan McDermid Syndrome Includes Symptoms of Affective Disorder, Psychosis, and Catatonia**

Presenter: Milena Andzelm & Tesi Kohlenberg
Authors: Asli Sahin[1], Audrey Thurm, PhD[1,2], Leslie Manso, MA[1], Sydney Jacobs, PhD[2], Siddharth Srivastava, MD[1,3], Milena Andzelm, MD, PhD[3]
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Hospital, Boston, MA USA, 3. Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA USA

Abstract: Background: Phelan McDermid Syndrome (PMS) is a rare genetic disorder that can present with the onset of complex neuropsychiatric symptoms after puberty. Serious Neuropsychiatric Illness (SNPI) is a proposed syndrome including major changes in mood, sleep and behavior, sometimes associated with loss of skills. We conducted an online study to characterize the patterns of SNPI in PMS patients. Methods: Social media outreach targeted English-speaking families of patients age 10 years or older with genetically-confirmed PMS, with or without psychiatric illness. Online surveys allowed caregivers to report on both psychiatric symptoms and skill loss, including age at onset, patterns of illness, and loss and recovery of skills. Surveys elicited lifetime experience of psychiatric symptoms, then further characterized SNPI based on symptoms endorsed as representing new or different emotional/behavioral problems with a clear change from baseline. Results: Caregiver reports were collected for 85 participants (mean age=22 years, 51% female). Of these, 69 (81%) met proposed criteria for SNPI, which included any psychiatric hospitalization, ≥3 symptoms of depression or of mania, or ≥2 core psychotic symptoms. Onset ranged from age 5 to 30 (mean age=13 years). The majority reported episodic affective illness, with 20% reporting core psychotic symptoms occurring during affective episodes, and 66% reporting symptoms consistent with catatonia. Multiple affective episodes were common with full return to premorbid emotional state in ~40%, and ~25% reporting ongoing symptoms. Discussion: These findings indicate that severe neuropsychiatric illness in PMS involves multifaceted affective, psychotic and catatonic symptoms, often starting around puberty and including multiple lifetime episodes. SNPI is often accompanied by loss of skills, although timing and degree of recovery differs. More research is needed to explore potential treatments and prevention of these serious symptoms and sequelae in individuals with PMS.

17. **Title: Zebrafish Reveal Serotonergic and Noradrenergic Mechanisms Underlying Phelan-McDermid Syndrome Phenotypes**

Presenter: Adhikansh Jain

Authors: Adhikansh Jain, PhD Candidate, Julia Dallman, PhD, Associate Professor of Biology

Affiliation: University of Miami

Abstract: Background: Despite detailed phenotypic characterization of PMS, the mechanistic links between SHANK3 haploinsufficiency, neuromodulator signaling, and phenotypes remain unclear. We leverage zebrafish (Danio rerio) harboring loss-of-function shank3 mutations to dissect these mechanisms. Zebrafish provide a uniquely tractable system due to their conserved serotonergic and noradrenergic circuits, transparent bodies, and quantifiable behaviors such as gut motility, sleep-wake cycles, and sensorimotor responses, enabling molecular, anatomical, and behavioral interrogation. One potential unifying mechanism is serotonin, a neurotransmitter involved in synaptic activity, mood regulation, and gut motility. Prior studies in our lab show reduced serotonin in the gut of shank3 mutants, and a smaller hindbrain, an area rich in serotonergic neurons. Interestingly, the locus coeruleus, the brain's primary source of norepinephrine, was enlarged in mutants, suggesting noradrenergic/serotonergic dysregulation, particularly in sleep/arousal.

Methods: We focused on the molecular underpinnings of these disruptions using RNA sequencing (RNA-seq) in 6-day-old zebrafish larvae. A comprehensive transcriptomic database was generated, profiling the gut and brain, with emphasis on serotonin-associated genes in the gut and noradrenaline-related pathways in the brain. This approach enables systematic identification of transcriptional changes caused by SHANK3 mutations, providing insight into how neurotransmitter signaling is altered at the molecular level in PMS. Results: RNA-seq revealed downregulation of multiple serotonin pathway genes in the gut of shank3 mutants, consistent with previously observed reductions in serotonin levels. In the brain, several genes involved in noradrenaline synthesis and signaling were altered, corresponding with morphological changes in the locus coeruleus. These findings demonstrate tissue-specific dysregulation of key neuromodulators relevant to sensory, motor, and sleep-related phenotypes in PMS. Discussion: By profiling transcriptional changes across gut and brain, this study reveals neurotransmitter-specific dysregulation in PMS and highlights zebrafish as a model for autism-relevant mechanisms. The RNA-seq database provides a resource to explore how SHANK3 mutations impact serotonergic and noradrenergic pathways during early development.

18. Title: Identifying translational sleep biomarkers in autism

Presenter: Shantanu Jadhav
Authors: Mingxin Ding[1], Diego Morandi Zerpa[1], Dara Manoach[2], Shantanu Jadhav[1]
Affiliations: Brandeis University, MGH

Abstract: Sleep disturbances are reported in up to ~80% of children with autism (Oyane and Bjorvatn, 2005). The presence of sleep disturbances in humans with genetic mutations linked to autism, including Phelan McDermid Syndrome (Moffitt et al., 2023), and in rodents with the same mutations, including Shank3 (Ingiosi et al.,2019), indicates that sleep disturbances reflect the pathophysiology of autism that may alter brain development. Understanding the neural basis of sleep disturbances in autism is a critical step towards effective treatment. During NREM sleep, the coordination of cortical slow oscillations (SOs), thalamocortical spindles, and hippocampal sharp-wave ripples is required for sleep-dependent memory consolidation (Brodt et al., 2023). Recent studies suggest that disrupted coordination of these brain rhythms may contribute to sleep impairments. Children with autism have reduced spindles and impaired coordination of spindles with SOs, and spindle deficits predicted worse sleep quality, consistent with the well-established role of spindles in preventing arousals (Mylonas et al., 2022). This leads us to hypothesize that deficits in thalamo-cortical-hippocampal circuits contribute to disrupted brain rhythms and sleep in autism. We are therefore conducting complementary human and rodent studies of network oscillatory dynamics during sleep and wake to identify translational sleep biomarkers for intervention studies. We use recently developed monogenic rat models, including Shank3 rats, to examine neural activity in deep brain structures using multielectrode in vivo physiology. In initial studies, we recorded activity from hippocampus and medial prefrontal cortex in Shank3 and Fragile-X adolescent rats (P30-P60). We characterized occurrence of NREM and REM sleep stages, quantified the occurrence of spindle-SOs in cortical networks, and sharp-wave ripples in hippocampal networks. We also characterized spiking activity of individual neurons and their recruitment by sleep oscillations. Our initial results

suggest that sleep neurophysiological biomarkers differ across genetic syndromes associated with autism.

19. **Title: A comparative approach for studying vocal communication impairments in autism and Phelan-McDermid syndrome**

Presenter: Joseph Del Rosario

Authors: Joseph Del Rosario[1], Zihua Chen[1], Rayee Wang[2], Helen Tager-Flusberg[3], Benjamin Scott[3], Michael A. Long[1]

Affiliations: 1. NYU Langone, 2. NYU, 3. Boston University

Abstract: Vocal communication impairments are a core feature of autism spectrum disorder (ASD) and related conditions including Phelan-McDermid Syndrome (PMS). Despite the prevalence of symptoms related to natural language use, the conversational capabilities in individuals affected by ASD has been severely understudied. Additionally, the lack of an animal model for understanding the relevant neural mechanisms underlying interactive communication has precluded a mechanistic study of the disrupted sensorimotor processes in ASD. To address these critical needs, we are bridging human clinical data and systems neuroscience to advance our mechanistic understanding of the neural circuits supporting vocal interactions and their disruption in ASD. First, we apply speech analysis tools developed by our lab to quantify turn-taking during natural conversational speech in ASD (including PMS) individuals. Early results indicate ASD individuals exhibit heterogeneous interactive vocal deficits compared to age-matched controls. Second, we leverage an animal model – the singing mouse (Scotinomys teguina) – to investigate the sensorimotor dynamics underlying naturalistic vocal exchanges, or 'counter-singing'. Unlike standard laboratory mice, singing mice produce structured audible vocalizations and engage in rapid counter-singing with conspecific vocal partners. We recently identified the orofacial motor cortex (OMC) as essential for this behavior as OMC inactivation abolishes rapid vocal responses. We are beginning to record OMC activity during counter-singing to understand the role of individual cortical neurons for vocal communication. Third, we have created an infrastructure to create a singing mouse model of ASD to explore their interactive vocal capabilities and accompanying neural impairments. Preliminary results indicate the singing mouse is amenable to standard genetic engineering strategies (e.g., CRISPR) which allow for manipulation of ASD-risk genes (including SHANK3, a gene that if mutated can result in PMS). Altogether, our human and animal work will provide unparalleled insight into the cortical neural drivers impairing communication behaviors in ASD individuals.

20. **Title: SHANK3 beyond the synapse, at the cilium**

Presenter: Delfina González

Authors: Delfina González, PhD[1], Ethel Bader[1], Catherine Nguyen[1] , Helen Willsey, PhD[1,2]

Affiliations: 1. Department of Psychiatry & Behavioral Sciences, UCSF, 2. Weill Institute for Neurosciences and Biohub-San Francisco

Abstract: Background: Pathogenic variants in SHANK3 cause Phelan-McDermid Syndrome (PMS), characterized by developmental and speech delays and regression, intellectual disabilities, autism, microcephaly, sleep disruption, seizures, GI problems, hypotonia, and a variety of dysmorphic features. The symptomatology of PMS is

ascribed to SHANK3's well-characterized role in neurotransmission through its role as a synaptic scaffolding protein. Recently, our lab discovered that SHANK3 also localizes to the cilium, a membrane-bound organelle critical for neurogenesis, neuronal excitability, and broadscale organ development. Therefore, we hypothesize that SHANK3 has developmental roles beyond the synapse, at the cilium. Methods: We tested this hypothesis in Xenopus (frog) using expression, localization, and loss-of-function approaches. SHANK3 mRNA expression was mapped using *in situ* hybridization and protein localization was assessed by immunofluorescence. Loss of function was induced by embryonic injection of translation-blocking morpholino antisense oligo nucleotides. We then assessed ciliary, organismal, and organ development. Results: SHANK3 mRNA is expressed in many tissues beyond the brain, including ciliated tissues. SHANK3 protein localizes to ciliary axonemes and basal bodies and its disruption causes ciliogenesis defects. At the organ and organismal levels, perturbing SHANK3 leads to decreased brain size, abnormal kidney development, and loss of motility. Discussion: These results demonstrate that SHANK3 has a role in ciliation in Xenopus, potentially identifying a new role beyond the synapse. The observed loss of ciliation suggests a model where SHANK3 scaffolds machinery required for ciliogenesis. This loss of ciliation may disrupt signaling pathways critical for neurogenesis and innervation, perturbing brain development and motility. These results suggest that interventions targeting a non-synaptic SHANK3 function at cilia can expand the therapeutic toolbox used for PMS patient treatment.

21. **Title: PYC-002: an RNA drug candidate for the treatment of Phelan-McDermid Syndrome**

Presenter: Dulce B. Vargas-Landin
Authors: Dulce B. Vargas-Landin, Abbie Francis, Wontaek Oh, Priyanka Sai, Rungtiwa Nutalai, Tracy Chai, Tanisha Verma, Philipp Bayer, Alexander de Bont, Jeremy Ash, Adam D. Martin, Maria Kerfoot, Sasiwimon Utama, Janya Grainok
Affiliation: PYC Therapeutics
Abstract: Background: Phelan-McDermid syndrome (PMS) is a severe neurodevelopmental disorder caused by the deletion of, or a pathogenic sequence variant in, one copy of the SHANK3 gene leading to haploinsufficiency of the SHANK3 protein. SHANK3 is a scaffolding protein critical for the structure, integrity and function of neuronal communication across the brain. SHANK3 is expressed in brain regions essential for learning and cognition, such as the hippocampus and prefrontal cortex. Its postnatal and lifelong expression provides a broad window for therapeutic intervention, from early childhood to adulthood. Despite its impact and prevalence, no disease-modifying therapies are currently available. To address this unmet need, PYC Therapeutics is developing an RNA drug candidate, PYC-002, to specifically target SHANK3 haploinsufficiency in PMS. PYC-002 is an antisense oligonucleotide, that binds to the RNA made by the remaining healthy SHANK3 gene copy in PMS. Its binding to SHANK3 RNA increases the production of the SHANK3 protein. Methods: Multiple PMS patient-derived iPSC-neurons were used to evaluate PYC-002 efficacy at protein (by protein quantification assays) and neuronal functional (by neuronal signalling assays) levels. Additionally, studies in wild-type Sprague-Dawley rats and cynomolgus monkeys injected intrathecally with PYC-002 were used to evaluate the biodistribution, safety and tolerability of PYC-002 over time. Results: In

patient-derived iPSC-neurons, PYC-002 treatment increased total SHANK3 protein expression and synapse density towards healthy levels, suggesting an improved neuronal synaptic structure. This synaptic improvement was accompanied by an enhanced function in neuronal signalling. Using the clinical route of administration, intrathecal injection, PYC-002 was found safe and well tolerated by both rats and monkeys, and successfully distributed to the critical brain regions implicated in PMS. Conclusion: Overall, this efficacy, biodistribution and safety data supports the advancement of PYC-002 drug candidate to a clinical stage.

22. **Title: A Longitudinal Caregiver-Reported Natural History Study to Map Developmental Milestone Trajectories in Phelan-McDermid Syndrome**

Presenter: Brian Moy

Authors: Dan Gallo[1], Tessa Clarkson[1,2], Gina Newton[1], Shouryadeep Sivastava[1], Amanda Truesdale[1], April Dovholuk[1], Kate Neer[1], Blair Ornstein[1], and Brian Moy[1]

Affiliations: 1. Jaguar Gene Therapy, LLC, Lake Forest, IL, 2. Psychlomere, Littleton, CO

Abstract: Background: Phelan-McDermid syndrome (PMS) is a rare, heterogeneous neurodevelopmental disorder marked by profound developmental delays, frequent non-attainment of developmental milestones, and risk of regression across communication, motor, social, and self-care domains. Recent large-scale natural history analyses, including a 2025 study led by Farmer and colleagues integrating registry-based caregiver reports and clinician-led longitudinal assessments, demonstrate that many individuals with PMS do not attain foundational developmental milestones. They also found that loss of previously acquired skills, particularly language, is common and often not fully regained. As new investigational treatments for PMS move forward in development, these findings underscore the need for clinical trial outcome strategies that can evaluate meaningful change, while accounting for differences in developmental trajectories across patients. Methods: To establish a robust reference framework for milestone-based outcome strategies, Jaguar Gene Therapy is initiating a longitudinal, non-interventional natural history study enrolling a minimum of 200 caregivers of individuals with PMS aged 2-30 years. Study data will be collected using a modular, web-based survey administered at baseline, 6 months, and 12 months. Caregivers will report milestone gains, losses, and regains within core functional domains, along with the perceived meaningfulness of each milestone in daily life. To reduce recall bias, caregivers will upload corroborative materials (e.g., medical or therapy records, videos, photographs), which will be reviewed by qualified clinicians for verification or adjudication. Analyses will characterize age-dependent milestone trajectories using cumulative incidence methods, explore the impact of covariates (e.g., genetics, structured therapy, disease severity) on attainment, and identify developmental plateaus through simulation-based approaches. Conclusions: Through caregiver reports, this natural history dataset is intended to provide novel insights into developmental milestone attainment and clinically meaningful changes in PMS. These data will help contextualize improvements observed in the JAG201 gene therapy program for PMS and further inform a patient-centered development pathway for JAG201.

23. **Title: What You Should Know about PMSF Membership and the PMS DataHub Data Registry**

Presenter: Lauren Schmitt*, Presented by: Kathryn Fiscus
Authors: Lauren M. Schmitt, Meagan C. Hutchinson, Katherine Still, Megan O'Boyle, Kathryn Fiscus
Affiliation: Phelan-McDermid Syndrome Foundation
Abstract: The Phelan-McDermid Syndrome Foundation (PMSF) offers two complementary programs that serve distinct purposes: PMSF Membership and the PMS DataHub. PMSF Membership is a free community resource that connects families with support services, educational programs, and organizational communications, including general research recruitment announcements. In contrast, the PMS DataHub is a research-focused registry developed to support natural history studies and clinical trial recruitment through the collection of comprehensive participant data, including medical records, medication and symptom tracking, syndrome-specific health surveys, and professionally curated genetic reports. Unlike standard membership, genetic reports submitted to the DataHub are reviewed and classified by genetic counselors using a standardized curation process. The registry currently includes approximately 1,700 participants from 66 countries, with about 800 participants residing in the United States, and contains more than 800 curated genetic reports. In addition, we will highlight presence or absence of key clinical features of Phelan-McDermid syndrome as well as distribution of genotype across our data registry participants.